

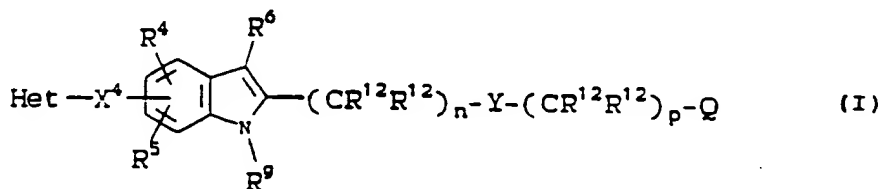
PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁵ : C07D 401/12, A61K 31/47	A1	(11) International Publication Number: WO 93/25546 (43) International Publication Date: 23 December 1993 (23.12.93)
(21) International Application Number: PCT/CA93/00253 (22) International Filing Date: 16 June 1993 (16.06.93) (30) Priority data: 899,399 17 June 1992 (17.06.92) US (60) Parent Application or Grant (63) Related by Continuation US 899,399 (CIP) Filed on 17 June 1992 (17.06.92) (71) Applicant (for all designated States except US): MERCK FROSST CANADA INC. [CA/CA]; 16711 Trans-Canada Highway, Kirkland, Quebec H9H 3L1 (CA).	(72) Inventor; and (75) Inventor/Applicant (for US only) : FRENETTE, Richard [CA/CA]; 1915 De Limbourg, Vimont, Laval, PQ H7M 4S7 (CA). (74) Agent: MURPHY, Kevin, P.; Swabey, Ogilvy, Renault, Suite 800, 1001 de Maisonneuve, West, Montreal, Que- bec H3A 3C8 (CA). (81) Designated States: AU, BB, BG, BR, CA, CZ, FI, HU, JP, KR, KZ, LK, MG, MN, MW, NO, NZ, PL, RO, RU, SD, SK, UA, US, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published With international search report.	

(54) Title: BICYCLIC(AZAAROMATIC)INDOLES AS INHIBITORS OF LEUKOTRIENE BIOSYNTHESIS



(57) Abstract

Compounds having formula (I) wherein Het is ArR¹R²R³, Ar is a bicyclic aromatic 8- to 10-membered ring containing 1 to 3 N atoms, the tetrahydro derivatives thereof, and the N-oxides thereof, are inhibitors of leukotriene biosynthesis. These compounds are useful as anti-asthmatic, anti-allergic, anti-inflammatory, and cytoprotective agents. They are also useful in treating diarrhea, hypertension, angina, platelet aggregation, cerebral spasm, premature labor, spontaneous abortion, dysmenorrhea, and migraine.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	FR	France	MR	Mauritania
AU	Australia	GA	Gabon	MW	Malawi
BB	Barbados	GB	United Kingdom	NL	Netherlands
BE	Belgium	GN	Guinea	NO	Norway
BF	Burkina Faso	GR	Greece	NZ	New Zealand
BG	Bulgaria	HU	Hungary	PL	Poland
BJ	Benin	IE	Ireland	PT	Portugal
BR	Brazil	IT	Italy	RO	Romania
CA	Canada	JP	Japan	RU	Russian Federation
CF	Central African Republic	KP	Democratic People's Republic of Korea	SD	Sudan
CG	Congo	KR	Republic of Korea	SE	Sweden
CH	Switzerland	KZ	Kazakhstan	SK	Slovak Republic
CI	Côte d'Ivoire	LI	Liechtenstein	SN	Senegal
CM	Cameroon	LK	Sri Lanka	SU	Soviet Union
CS	Czechoslovakia	LU	Luxembourg	TD	Chad
CZ	Czech Republic	MC	Monaco	TC	Togo
DE	Germany	MG	Madagascar	UA	Ukraine
DK	Denmark	ML	Mali	US	United States of America
ES	Spain	MN	Mongolia	VN	Viet Nam
FI	Finland				

5

- 1 -

10 TITLE OF THE INVENTION
BICYCLIC(AZAAROMATIC)INDOLES AS INHIBITORS OF
LEUKOTRIENE BIOSYNTHESIS

BACKGROUND OF THE INVENTION

15 European Patent Applications 166,591 and
275,667 disclose a series of indole-based compounds
with activity as prostaglandin antagonists and
inhibitors of leukotriene biosynthesis respectively.
In EP 181,568 and EP 200,101 are disclosed a series
20 of compounds, containing two aromatic nuclei, which
are described as possessing activity as lipxygenase
inhibitors. In EP 279,263 is disclosed a series of
indoles, benzofurans and benzothiophenes which are
described as possessing activity as lipxygenase

25

30

- 2 -

inhibitors. U.S. Patent 4,629,733 describes novel indolinones which are antithrombotic and inhibit both phosphodiesterase and tumor metastasis. The chemical preparation of quinolyllindoles is referred to by
5 Sheinkman, et al., Chem. Ab., Vol. 67, 54017 (1967), without mentioning any utility for such compounds. A number of N-acyl derivatives of indole-3-acetic acid are described as potential anti-inflammatory agents by Biniecki, et al., Chem. Ab., Vol. 98, 197936
10 (1983), by Pakula, et al., Chem. Ab., Vol. 105, 190835 (1986), and in British Pat. Spec. 1,228,848.

EP 419,049 (March 27, 1991) teaches (quinolin-2-ylmethoxy)indoles as inhibitors of leukotriene biosynthesis. WO 92/03132
15 (March 5, 1992) teaches indole derivatives as inhibitors of leukotriene biosynthesis.

SUMMARY OF THE INVENTION

The present invention relates to bicyclic
20 (azaaromatic) indoles having activity as leukotriene biosynthesis inhibitors, to methods for their preparation, and to methods and pharmaceutical formulations for using these compounds in mammals (especially humans).

25 Because of their activity as leukotriene biosynthesis inhibitors, the compounds of the present invention are useful as anti-asthmatic, anti-allergic, and anti-inflammatory agents and are useful in treating allergic rhinitis and chronic bronchitis
30 and for amelioration of skin diseases like psoriasis and atopic eczema. These compounds are also useful to inhibit the pathologic actions of leukotrienes on the cardiovascular and vascular systems for example,

- 3 -

actions such as result in angina or endotoxin shock. The compounds of the present invention are useful in the treatment of inflammatory and allergic diseases of the eye, including allergic conjunctivitis. The
5 compounds are also useful as cytoprotective agents and for the treatment of migraine headache.

Thus, the compounds of the present invention may also be used to treat or prevent mammalian (especially, human) disease states such as erosive
10 gastritis; erosive esophagitis; inflammatory bowel disease; ethanol-induced hemorrhagic erosions; hepatic ischemia; noxious agent-induced damage or necrosis of hepatic, pancreatic, renal, or myocardial tissue; liver parenchymal damage caused by hepatotoxic
15 agents such as CCl_4 and D-galactosamine; ischemic renal failure; disease-induced hepatic damage; bile salt induced pancreatic or gastric damage; trauma- or stress-induced cell damage; and glycerol-induced renal failure.

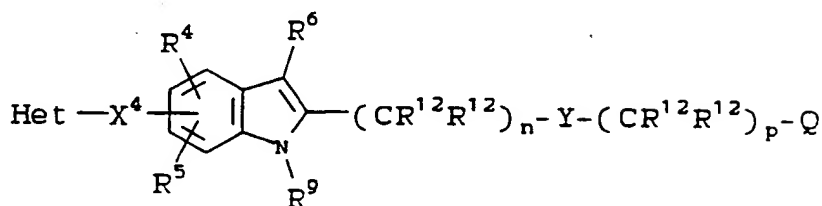
20 The compounds of this invention are inhibitors of the biosynthesis of 5-lipoxygenase metabolites of arachidonic acid, such as 5-HPETE, 5-HETE and the leukotrienes. Leukotrienes B_4 , C_4 , D_4 and E_4 are known to contribute to various disease
25 conditions such as asthma, psoriasis, pain, ulcers and systemic anaphylaxis. Thus inhibition of the synthesis of such compounds will alleviate these and other leukotriene-related disease states.

30

- 4 -

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides novel compounds of the formula I:



15 wherein:

Het is $\text{ArR}^1\text{R}^2\text{R}^3$;

Ar is a bicyclic aromatic 8- to 10- membered ring containing 1 to 3 N atoms, the tetrahydro derivatives thereof, and the N-oxides thereof;

20

R^1 , R^2 , R^3 , R^4 , R^5 , and R^{11} are independently hydrogen, halogen, perhalo lower alkenyl, lower alkyl, lower alkenyl, lower alkynyl, $-\text{CF}_3$, $-\text{CN}$, $-\text{NO}_2$, $-\text{N}_3$, $-\text{C}(\text{OH})\text{R}^{12}\text{R}^{12}$, $-\text{CO}_2\text{R}^{13}$, $-\text{SR}^{15}$, $-\text{S}(\text{O})\text{R}^{15}$, $-\text{S}(\text{O})_2\text{R}^{15}$, $-\text{S}(\text{O})_2\text{NR}^{16}\text{R}^{16}$, $-\text{OR}^{16}$, $-\text{NR}^{16}\text{R}^{16}$, $-\text{NR}^{13}\text{CONR}^{16}\text{R}^{16}$, $-\text{COR}^{17}$, $\text{CONR}^{16}\text{R}^{16}$, or $-(\text{CH}_2)_t\text{R}^{22}$;

25

R^6 is hydrogen, $-\text{CH}_3$, CF_3 , $-\text{C}(\text{O})\text{H}$, X^1-R^7 or X^2-R^8 ;

30

- 5 -

R^7 and R^{10} are independently alkyl, alkenyl,
 $-(CH_2)_uPh(R^{11})_2$ or $-(CH_2)_uTh(R^{11})_2$;

R^8 is $-CF_3$ or R^7 ;

R^9 is hydrogen or X^3-R^{10} ;

each R^{12} is independently hydrogen or lower alkyl, or
two R^{12} 's on same carbon atom are joined to
form a cycloalkyl ring of 3 to 6 carbon
atoms;

R^{13} is hydrogen, lower alkyl or $-CH_2R^{22}$;

R^{14} is lower alkyl or $-(CH_2)_rR^{22}$;

R^{15} is $-CF_3$ or R^{14} ;

R^{16} is hydrogen, OH, $-COR^{17}$, R^{14} , or two R^{16} 's on
the same nitrogen may be joined to form a
monocyclic heterocyclic ring of 4 to 6 atoms
containing up to 2 heteroatoms chosen from
O, S, or N;

R^{17} is hydrogen, $-CF_3$, lower alkyl, lower alkenyl,
lower alkynyl or $-(CH_2)_rR^{22}$;

R^{18} is $-(CH_2)_s-C(R^{19}R^{19})-(CH_2)_s-R^{20}$ or
 $-CH_2CONR^{16}R^{16}$;

R^{19} is hydrogen or lower alkyl;

- 6 -

- 5 R²⁰ is a) a monocyclic or bicyclic heterocyclic
 ring containing from 3 to 9 nuclear
 carbon atoms and 1 or 2 nuclear
 hetero-atoms selected from N, S or O
 and with each ring in the heterocyclic
 radical being formed of 5 or 6 atoms, or
 b) the radical W-R²¹;
- 10 R²¹ is alkyl or -COR²⁴;
- R²² is phenyl substituted with 1 or 2 R²³ groups;
- 15 R²³ is hydrogen, halogen, lower alkyl, lower
 alkoxy, lower alkylthio, lower
 alkylsulfonyl, lower alkylcarbonyl, -CF₃,
 -CN, -NO₂ or -N₃;
- 20 R²⁴ is alkyl, cycloalkyl, or monocyclic
 monoheterocyclic ring;
- R²⁵ is the residual structure of a standard amino
 acid, or R¹⁹ and R²⁵ attached to the same N
 can cyclize to form a proline residue;
- 25 R²⁶ is hydrogen or lower alkyl;
- R²⁷ is lower alkyl or R²⁶ and R²⁷ on the same
 carbon are joined to form a cycloalkyl ring
 of 3 to 6 carbon atoms;
- 30 m is 1 to 3;
 n is 0 to 3;
 p is 1 to 3 when m is 1;

- 7 -

- p is 0 to 3 when m is 0;
 r is 0 to 2;
 s is 0 to 3;
 t is 0 to 2;
 5 u is 0 to 3;
 W is 0, S or NR¹⁶
 X¹ is 0 or NR¹⁶;
 X² is CO, CR¹²R¹², S, S(O), or S(O)₂;
 X³ is CO, CR¹²R¹², S(O)₂, or a bond;
 10 X⁴ is CR²⁶=CR²⁷, CR²⁷=R²⁶, CR²⁶R²⁷Y¹, or Y¹CR²⁷R²⁶;
 Y is X¹, X², O-NR¹⁶, NR¹⁶-O or a bond;
 Y¹ is 0, S, S(O)₂, or CR²⁶R²⁶;

 15 Q is -CO₂R¹³, -CONES(O)₂R¹⁵, -NHS(O)₂R¹⁵, CN,
 -S(O)₂NHR¹⁶, -CONR¹⁶R¹⁶, -CO₂R¹⁸,
 -CONR¹⁹R²⁵, -CR¹²R¹²OH, or 1H- or
 2H-tetrazol-5-yl, -NR¹⁶R¹⁶, -NR¹⁶CONR¹⁶R¹⁶,
 -C(=NR¹⁶)R¹⁷, -NR¹⁶(CH₂)_mNR¹⁶R¹⁶,
 -N(R¹⁶)(CH₂)_mNR¹⁶CONR¹⁶R¹⁶,
 20 -CON(R¹⁶)(CH₂)_mNR¹⁶R¹⁶,
 -CON(R¹⁶)(CH₂)_mNR¹⁶CONR¹⁶R¹⁶;

or a pharmaceutically acceptable salt thereof.

- 25 A preferred embodiment of Formula I is that
 in which X⁴ is CHMe-O, and the remaining substituents
 are as defined for Formula I.

- 30 Another preferred embodiment of Formula I is
 that in which R¹ and R² are independently H or F;
 R³, R⁴, and R⁵ are hydrogen;
 R⁶ is X²-R⁸;
 R⁸ is R⁷;

- 8 -

- R⁹ is R¹⁰;
R¹¹ is hydrogen or halogen;
m is 0;
n is 1 to 3;
5 u is 0 in R⁷ and 1 in R¹⁰;
X² is CR¹²R¹², S or CO;
X⁴ is CR²⁶R²⁷-Y¹;
Y¹ is O;
- 10 Q is -CO₂R¹³ or 1-H or 2H-tetrazol-5-yl; and the
remaining substituents are as defined for Formula I;
or a pharmaceutically acceptable salt thereof.

15 The preferred compounds of this invention
are as follows:

- (+) Sodium 3-[N-(p-chlorobenzyl)-3-(t-butylthio)-5-[1-(quinolin-2-yl)ethoxy]indol-2-yl]-2,2-dimethyl-
propanoate,
20
- (-) Sodium 3-[N-(p-chlorobenzyl)-3-(t-butylthio)-5-[1-(quinolin-2-yl)ethoxy]indol-2-yl]-2,2-dimethyl-
propanoate,
- 25 (+) Sodium 3-[N-(p-chlorobenzyl)-3-(t-butylthio)-5-[1-(quinolin-2-yl)butoxy]indol-2-yl]-2,2-dimethyl-
propanoate, or
- 30 (-) Sodium 3-[N-(p-chlorobenzyl)-3-(t-butylthio)-5-[1-(quinolin-2-yl)butoxy]indol-2-yl]-2,2-dimethyl-
propanoate,

or a pharmaceutically acceptable salt thereof.

- 9 -

Definitions

The following abbreviations have the indicated meanings:

5

Me = methyl

Bn = benzyl

Ph = phenyl

DIBAL-H = diisobutyl aluminum hydride

10

HMPA = hexamethylphosphorotriamide

KHMDS = potassium hexamethyldisilazide

t-Bu = tert-butyl

i-Pr = isopropyl

c-C₆H₁₁ = cyclohexyl

15

c-Pr = cyclopropyl

c- = cyclo

Ac = acetyl

Tz = 1H- or 2H- tetrazol-5-yl

Th = 2- or 3- thienyl

20

c-C₅H₉ = cyclopentyl

LDA = lithium diisopropylamide

1-Ad = 1-adamantyl

NBS = N-bromosuccinimide

NCS = N-chlorosuccinimide

25

Alkyl, alkenyl, and alkynyl are intended to include linear, branched, and cyclic structures and combinations thereof.

30

"Alkyl" includes "lower alkyl" and extends to cover carbon fragments having up to 20 carbon atoms. Examples of alkyl groups include octyl, nonyl, norbornyl, undecyl, dodecyl, tridecyl,

- 10 -

tetradecyl, pentadecyl, eicosyl, 3,7-diethyl-2,2-dimethyl-4-propylnonyl, cyclododecyl, adamantyl, and the like.

5 "Lower alkyl" means alkyl groups of from 1 to 7 carbon atoms. Examples of lower alkyl groups include methyl, ethyl, propyl, isopropyl, butyl, sec- and tert-butyl, pentyl, hexyl, heptyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, 2-methylcyclopropyl, cyclopropylmethyl, and the like.

10 "Cycloalkyl" refers to a hydrocarbon ring having from 3 to 7 carbon atoms. Examples of cycloalkyl groups are cyclopropyl, cyclopentyl, cycloheptyl, and the like.

15 "Lower alkenyl" means alkenyl groups of 2 to 7 carbon atoms. Examples of lower alkenyl groups include vinyl, allyl, isopropenyl, pentenyl, hexenyl, heptenyl, cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, 1-propenyl, 2-butenyl, 2-methyl-2-butenyl, and the like.

20 "Lower alkynyl" means alkynyl groups of 2 to 7 carbon atoms. Examples of lower alkynyl groups include ethynyl, propargyl, 3-methyl-1-pentyne, 2-heptyne, and the like.

25 "Lower alkoxy" means alkoxy groups of from 1 to 7 carbon atoms of a straight, branched, or cyclic configuration. Examples of lower alkoxy groups include methoxy, ethoxy, propoxy, isopropoxy, cyclopropyloxy, cyclohexyloxy, and the like.

30 "Lower alkylthio" means alkylthio groups of from 1 to 7 carbon atoms of a straight, branched or cyclic configuration. Examples of lower alkylthio groups include methylthio, propylthio, isopropylthio, cycloheptylthio, etc. By way of illustration, the propylthio group signifies $-SCH_2CH_2CH_3$.

- 11 -

The term "monocyclic monoheterocyclic ring" which defines R^{24} means monocyclic groups of 5 to 7 members containing only 1 heteroatom selected from N, S or O in the ring. Examples include tetrahydro-
5 furan, tetrahydrothiophene, pyrrolidine, piperidine, tetrahydropyran, and the like.

The term "monocyclic or bicyclic heterocyclic ring" which defines R^{20} may be 2,5-dioxo-1-pyrrolidinyl, (3-pyridinylcarbonyl)
10 amino, 1,3-dihydro-1,3-dioxo-2H-isoindol-2-yl, 1,3-dihydro-2H-isoindol-2-yl, 2,4-imidazolin-1-yl, 2,6-piperidinedion-1-yl, 2-imidazolyl, 2-oxo-1,3-dioxolen-4-yl, piperidin-1-yl, morpholin-1-yl, piperazin-1-yl, and the like.

15 "Bicyclic aromatic 8- to 10-membered ring containing 1 to 3 N atoms, the tetrahydro derivatives thereof and the N-oxides thereof" which defines "Ar" may include indole, indolizine, indazole, benzimidazole, imidazo [1,2-a]pyridine, imidazo[5,4-c]pyri-
20 dine, pyrrolo[3,2-b]pyridine, quinoline, isoquinoline, cinnoline, quinazoline, quinoxaline, 1,8-naphthyridine, pyrido[2,3-b]pyrazine, their tetrahydro derivatives, and the like.

The point of attachment of any heterocyclic
25 ring may be at any free valence of the ring.

The term standard amino acid is employed to include the following amino acids: alanine, asparagine, aspartic acid, arginine, cysteine, glutamic acid, glutamine, glycine, histidine,
30 isoleucine, leucine, lysine, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine and valine. (See F.H.C. Crick, Symposium of the Society for Experimental Biology, 1958 (12) p. 140.)

- 12 -

It is understood that R^1 and R^2 may be located at any free positions of Ar.

The terms $\text{Ph}(R^{11})_2$ and $\text{Th}(R^{11})_2$ indicate a phenyl or thienyl group substituted with two R^{11} substituents.

Halogen includes F, Cl, Br, and I.

It is intended that the definitions of any substituent (e.g., R^1 , R^2 , R^{16} , $\text{Ph}(R^{11})_2$, etc.) in a particular molecule be independent of its definitions elsewhere in the molecule. Thus, $-\text{NR}^{16}\text{R}^{16}$ represents $-\text{NEH}$, $-\text{NHCH}_3$, $-\text{NHC}_6\text{H}_5$, etc.

The monocyclic heterocyclic rings formed when two R^{16} groups join through N include pyrrolidine, piperidine, morpholine, thiamorpholine, piperazine, and N-methylpiperazine.

The prodrug esters of Q (i.e., when $Q = \text{CO}_2\text{R}^{18}$) are intended to include the esters such as are described by Saari *et al.*, J. Med. Chem., 21, No. 8, 746-753 (1978), Sakamoto *et al.*, Chem. Pharm. Bull., 32, No. 6, 2241-2248 (1984) and Bundgaard *et al.*, J. Med. Chem., 30, No. 3, 451-454 (1987).

Some of the compounds described herein contain one or more asymmetric centers and may thus give rise to diastereomers and optical isomers. The present invention is meant to comprehend such possible diastereomers as well as their racemic and resolved, enantiomerically pure forms and pharmaceutically acceptable salts thereof.

The pharmaceutical compositions of the present invention comprise a compound of Formula I as an active ingredient or a pharmaceutically acceptable salt, thereof, and may also contain a pharmaceutically acceptable carrier and optionally.

- 13 -

other therapeutic ingredients. The term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic bases including inorganic bases and organic bases.

5 Salts derived from inorganic bases include aluminum, ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganic salts, manganous, potassium, sodium, zinc and the like. Particularly preferred are the ammonium, calcium, magnesium, potassium

10 and sodium salts. Salts derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion exchange resins,

15 such as arginine, betaine, caffeine, choline, N,N¹-dibenzylethylenediamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethylmorpholine, N-ethylpiperidine, glucamine, glucosamine, histidine,

20 hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine, tripropylamine, tromethamine and the like.

25 When the compound of the present invention is basic, salts may be prepared from pharmaceutically acceptable non-toxic acids, including inorganic and organic acids. Such acids include acetic, benzenesulfonic, benzoic, camphorsulfonic, citric,

30 ethanesulfonic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, pamoic, pantothenic, phosphoric, succinic, .

- 14 -

sulfuric, tartaric, p-toluenesulfonic acid and the like. Particularly preferred are citric, hydrobromic, hydrochloric, maleic, phosphoric, sulfuric and tartaric acids.

5 It will be understood that in the discussion of methods of treatment which follows, references to the compounds of Formula I are meant to also include the pharmaceutically acceptable salts.

10 The ability of the compounds of Formula I to inhibit biosynthesis of the leukotrienes makes them useful for inhibiting the symptoms induced by the leukotrienes in a human subject. This inhibition of the mammalian biosynthesis of leukotrienes indicates
15 that the compounds and pharmaceutical compositions thereof are useful to treat, prevent or ameliorate in mammals and especially in humans: 1) pulmonary conditions including diseases such as asthma, 2) allergies and allergic reactions such as allergic rhinitis, contact dermatitis, allergic
20 conjunctivitis, and the like, 3) inflammation such as arthritis or inflammatory bowel disease, 4) pain, 5) skin conditions such as psoriasis and the like, 6) cardiovascular conditions such as angina, endotoxin shock, and the like and 7) renal insufficiency
25 arising from ischaemia induced by immunological or chemical (cyclosporin) etiology, and that the compounds are cytoprotective agents.

 The cytoprotective activity of a compound may be observed in both animals and man by noting the
30 increased resistance of the gastrointestinal mucosa to the noxious effects of strong irritants, for example, the ulcerogenic effects of aspirin or indomethacin. In addition to lessening the effect of

- 15 -

non-steroidal anti-inflammatory drugs on the gastrointestinal tract, animal studies show that cytoprotective compounds will prevent gastric lesions induced by oral administration of strong acids,
5 strong bases, ethanol, hypertonic saline solutions and the like.

Two assays can be used to measure cytoprotective ability. These assays are; (A) an ethanol-induced lesion assay and (B) an
10 indomethacin-induced ulcer assay and are described in EP 140,684.

The magnitude of prophylactic or therapeutic dose of a compound of Formula I will, of course, vary with the nature of the severity of the condition to
15 be treated and with the particular compound of Formula I and its route of administration. It will also vary according to the age, weight and response of the individual patient. In general, the daily dose range for anti-asthmatic, anti-allergic or
20 anti-inflammatory use and generally, uses other than cytoprotection, lie within the range of from about 0.001 mg to about 100 mg per kg body weight of a mammal, preferably 0.01 mg to about 10 mg per kg, and most preferably 0.1 to 1 mg per kg, in single or
25 divided doses. On the other hand, it may be necessary to use dosages outside these limits in some cases.

For use where a composition for intravenous administration is employed, a suitable dosage range
30 for anti-asthmatic, anti-inflammatory or anti-allergic use is from about 0.001 mg to about 25 mg (preferably from 0.01 mg to about 1 mg) of a

- 16 -

compound of Formula I per kg of body weight per day
and for cytoprotective use from about 0.1 mg to about
100 mg (preferably from about 1 mg to about 100 mg
and more preferably from about 1 mg to about 10 mg)
5 of a compound of Formula I per kg of body weight per
day.

In the case where an oral composition is
employed, a suitable dosage range for anti-asthmatic,
anti-inflammatory or anti-allergic use is, e.g. from
10 about 0.01 mg to about 100 mg of a compound of
Formula I per kg of body weight per day, preferably
from about 0.1 mg to about 10 mg per kg and for
cytoprotective use from 0.1 mg to about 100 mg
(preferably from about 1 mg to about 100 mg and more
15 preferably from about 10 mg to about 100 mg) of a
compound of Formula I per kg of body weight per day.

For the treatment of diseases of the eye,
ophthalmic preparations for ocular administration
comprising 0.001-1% by weight solutions or
20 suspensions of the compounds of Formula I in an
acceptable ophthalmic formulation may be used.

The exact amount of a compound of the
Formula I to be used as a cytoprotective agent will
depend on, inter alia, whether it is being
25 administered to heal damaged cells or to avoid future
damage, on the nature of the damaged cells (e.g.,
gastrointestinal ulcerations vs. nephrotic necrosis),
and on the nature of the causative agent. An example
of the use of a compound of the Formula I in avoiding
30 future damage would be co-administration of a
compound of the Formula I with a non-steroidal
anti-inflammatory drug (NSAID) that might otherwise

- 17 -

cause such damage (for example, indomethacin). For such use, the compound of Formula I is administered from 30 minutes prior up to 30 minutes after administration of the NSAID. Preferably it is
5 administered prior to or simultaneously with the NSAID, (for example, in a combination dosage form).

Any suitable route of administration may be employed for providing a mammal, especially a human with an effective dosage of a compound of the present
10 invention. For example, oral, rectal, topical, parenteral, ocular, pulmonary, nasal, and the like may be employed. Dosage forms include tablets, troches, dispersions, suspensions, solutions, capsules, creams, ointments, aerosols, and the like.

15 The pharmaceutical compositions of the present invention comprise a compound of Formula I as an active ingredient or a pharmaceutically acceptable salt thereof, and may also contain a pharmaceutically acceptable carrier and optionally other therapeutic
20 ingredients. The term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic bases or acids including inorganic bases or acids and organic bases or acids.

The compositions include compositions
25 suitable for oral, rectal, topical, parenteral (including subcutaneous, intramuscular, and intravenous), ocular (ophthalmic), pulmonary (nasal or buccal inhalation), or nasal administration, although the most suitable route in any given case
30 will depend on the nature and severity of the conditions being treated and on the nature of the active ingredient. They may be conveniently presented in unit dosage form and prepared by any of the methods well-known in the art of pharmacy.

- 18 -

For administration by inhalation, the compounds of the present invention are conveniently delivered in the form of an aerosol spray presentation from pressurized packs or nebulisers. The compounds may also be delivered as powders which may be formulated and the powder composition may be inhaled with the aid of an insufflation powder inhaler device. The preferred delivery system for inhalation is a metered dose inhalation (MDI) aerosol, which may be formulated as a suspension or solution of Compound I in suitable propellants, such as fluorocarbons or hydrocarbons.

Suitable topical formulations of Compound I include transdermal devices, aerosols, creams, ointments, lotions, dusting powders, and the like.

In practical use, the compounds of Formula I can be combined as the active ingredient in intimate admixture with a pharmaceutical carrier according to conventional pharmaceutical compounding techniques. The carrier may take a wide variety of forms depending on the form of preparation desired for administration, e.g., oral or parenteral (including intravenous). In preparing the compositions for oral dosage form, any of the usual pharmaceutical media may be employed, such as, for example, water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents and the like in the case of oral liquid preparations, such as, for example, suspensions, elixirs and solutions; or carriers such as starches, sugars, microcrystalline cellulose, diluents, granulating agents, lubricants, binders, disintegrating agents and the like in the

- 19 -

case of oral solid preparations such as, for example, powders, capsules and tablets, with the solid oral preparations being preferred over the liquid preparations. Because of their ease of
5 administration, tablets and capsules represent the most advantageous oral dosage unit form in which case solid pharmaceutical carriers are obviously employed. If desired, tablets may be coated by standard aqueous or nonaqueous techniques.

10 In addition to the common dosage forms set out above, the compounds of Formula I may also be administered by controlled release means and/or delivery devices such as those described in U.S. Patent Nos. 3,845,770; 3,916,899; 3,536,809;
15 3,598,123; 3,630,200 and 4,008,719.

Pharmaceutical compositions of the present invention suitable for oral administration may be presented as discrete units such as capsules, cachets or tablets each containing a predetermined amount of
20 the active ingredient, as a powder or granules or as a solution or a suspension in an aqueous liquid, a non-aqueous liquid, an oil-in-water emulsion or a water-in-oil liquid emulsion. Such compositions may be prepared by any of the methods of pharmacy but all
25 methods include the step of bringing into association the active ingredient with the carrier which constitutes one or more necessary ingredients. In general, the compositions are prepared by uniformly and intimately admixing the active ingredient with
30 liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product into the desired presentation. For example, a tablet

- 20 -

may be prepared by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine, the active ingredient in a free-flowing form
5 such as powder or granules, optionally mixed with a binder, lubricant, inert diluent, surface active or dispersing agent. Molded tablets may be made by molding in a suitable machine, a mixture of the powdered compound moistened with an inert liquid
10 diluent. Desirably, each tablet contains from about 2.5 mg to about 500 mg of the active ingredient and each cachet or capsule contains from about 2.5 to about 500 mg of the active ingredient.

The following are examples of representative
15 pharmaceutical dosage forms for the compounds of Formula I:

<u>Injectable Suspension (I.M.)</u>		<u>mg/ml</u>
Compound of Formula I		10
20 Methylcellulose		5.0
Tween 80		0.5
Benzyl alcohol		9.0
Benzalkonium chloride		1.0
Water for injection		
25 to a total volume of 1 ml		
<u>Tablet</u>		<u>mg/tablet</u>
Compound of Formula I		25
Microcrystalline Cellulose		415
30 Providone		14.0
Pregelatinized Starch		43.5
Magnesium Stearate		<u>2.5</u>
		500

- 21 -

<u>Capsule</u>		<u>mg/capsule</u>
Compound of Formula I		25
Lactose Powder		573.5
5	Magnesium Stearate	<u>1.5</u>
		600
 <u>Aerosol</u>		 <u>Per canister</u>
Compound of Formula I		24 mg
10	Lecithin, NF Liquid Concentrate	1.2 mg
Trichlorofluoromethane, NF		4.025 gm
Dichlorodifluoromethane, NF		12.15 gm

15 In addition to the compounds of Formula I, the pharmaceutical compositions of the present invention can also contain other active ingredients, such as cyclooxygenase inhibitors, non-steroidal anti-inflammatory drugs (NSAIDs), peripheral analgesic agents such as zomepirac diflunisal and the like. The weight ratio of
20 the compound of the Formula I to the second active ingredient may be varied and will depend upon the effective dose of each ingredient. Generally, an effective dose of each will be used. Thus, for example, when a compound of the Formula I is combined with an NSAID
25 the weight ratio of the compound of the Formula I to the NSAID will generally range from about 1000:1 to about 1:1000, preferably about 200:1 to about 1:200. Combinations of a compound of the Formula I and other active ingredients will generally also be within the
30 aforementioned range, but in each case, an effective dose of each active ingredient should be used.

- 22 -

NSAIDs can be characterized into five groups:

- (1) the propionic acid derivatives;
- (2) the acetic acid derivatives;
- (3) the fenamic acid derivatives;
- 5 (4) the oxicams; and
- (5) the biphenylcarboxylic acid derivatives;

or a pharmaceutically acceptable salt thereof.

10 The propionic acid derivatives which may be used comprise: alminoprofen, benoxaprofen, bucloxic acid, carprofen, fenbufen, fenoprofen, fluprofen, flurbiprofen, ibuprofen, indoprofen, ketoprofen, miroprofen, naproxen, oxaprozin, piroprofen, prano-profen, suprofen, tiaprofenic acid, and
15 tioxaprofen. Structurally related propionic acid derivatives having similar analgesic and anti-inflammatory properties are also intended to be included in this group.

Thus, "propionic acid derivatives" as
20 defined herein are non-narcotic analgesics/non-steroidal anti-inflammatory drugs having a free $-\text{CH}(\text{CH}_3)\text{COOH}$ or $-\text{CH}_2\text{CH}_2\text{COOH}$ group (which optionally can be in the form of a pharmaceutically acceptable salt group, e.g.,
25 $-\text{CH}(\text{CH}_3)\text{COO}^-\text{Na}^+$ or $-\text{CH}_2\text{CH}_2\text{COO}^-\text{Na}^+$), typically attached directly or via a carbonyl function to a ring system, preferably to an aromatic ring system.

The acetic acid derivatives which may be
30 used comprise: indomethacin, which is a preferred NSAID, acetaminophen, alclufenac, clidanac, diclofenac, fenclofenac, fenclozic acid, fentiazac, furofenac, ibufenac, isoxepac, oxpinac, sulindac, tiopinac,

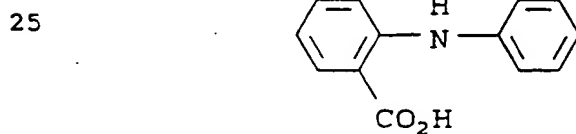
- 23 -

tolmetin, zidometacin and zomepirac. Structurally related acetic acid derivatives having similar analgesic and anti-inflammatory properties are also intended to be encompassed by this group.

5 Thus, "acetic acid derivatives" as defined herein are non-narcotic analgesics/non-steroidal anti-inflammatory drugs having a free $-\text{CH}_2\text{COOH}$ group (which optionally can be in the form of a pharmaceutically acceptable salt group, e.g.,
10 $-\text{CH}_2\text{COO}^-\text{Na}^+$), typically attached directly to a ring system, preferably to an aromatic or heteroaromatic ring system.

The fenamic acid derivatives which may be used comprise: flufenamic acid, meclofenamic acid,
15 mefenamic acid, niflumic acid and tolfenamic acid. Structurally related fenamic acid derivatives having similar analgesic and anti-inflammatory properties are also intended to be encompassed by this group.

20 Thus, "fenamic acid derivatives" as defined herein are non-narcotic analgesics/non-steroidal anti-inflammatory drugs which contain the basic structure:

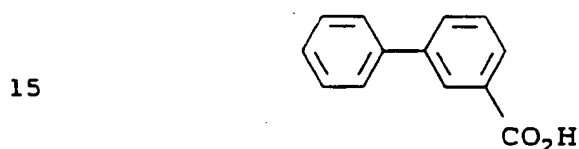


30 which can bear a variety of substituents and in which the free $-\text{COOH}$ group can be in the form of a pharmaceutically acceptable salt group, e.g., $-\text{COO}^-\text{Na}^+$.

- 24 -

The biphenylcarboxylic acid derivatives which can be used comprise: diflunisal and flufenisal. Structurally related biphenylcarboxylic acid derivatives having similar analgesic and anti-inflammatory properties are also intended to be encompassed by this group.

Thus, "biphenylcarboxylic acid derivatives" as defined herein are non-narcotic analgesics/non-steroidal anti-inflammatory drugs which contain the basic structure:



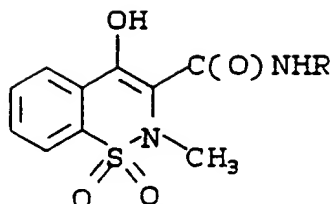
which can bear a variety of substituents and in which the free -COOH group can be in the form of a pharmaceutically acceptable salt group, e.g., -COO⁻Na⁺.

The oxicams which can be used in the present invention comprise: isoxicam, piroxicam, sudoxicam and tenoxicam. Structurally related oxicams having similar analgesic and anti-inflammatory properties are also intended to be encompassed by this group.

Thus, "oxicams" as defined herein are non narcotic analgesics/non-steroidal anti-inflammatory drugs which have the general formula:

30

- 25 -



wherein R is an aryl or heteroaryl ring system.

The following NSAIDs may also be used:

10 amfenac sodium, aminoprofen, anitrazafen,
antrafenine, auranofin, bendazac lysinate,
benzydanine, beprozin, broperamole, bufezolac,
cinmetacin, ciproquazone, cloximate, dazidamine,
15 deboxamet, delmetacin, detomidine, dexindoprofen,
diacerein, di-fisalamine, difenpyramide, emorfazone,
enfenamic acid, enolicam, epirizole, etersalate,
etodolac, etofenamate, fanetizole mesylate,
fenclorac, fendosal, fenflumizole, feprazone,
20 floctafenine, flunixin, flunoxaprofen, fluproquazone,
fopirtoline, fosfosal, furclopofen, glucametacin,
guaimesal, ibuproxam, isofezolac, isonixim,
isoprofen, isoxicam, lefetamine HCl, leflunomide,
lofemizole, lonazolac calcium, lotifazole,
25 loxoprofen, lysin clonixinate, meclofenamate sodium,
meseclazone, nabumetone, nictindole, nimesulide,
orpanoxin, oxametacin, oxapadol, perisoxal citrate,
pimeprofen, pimetacin, piproxen, pirazolac,
pirfenidone, proglumetacin maleate, proquazone,
30 pyridoxiprofen, sudoxicam, talmetacin, talniflumate,
tenoxicam, thiazolinobutazone, thielavin B, tiaramide
HCl, tiflamizole, timegadine, tolpadol, tryptamid and
ufenamate.

- 26 -

The following NSAIDs, designated by company code number (see e.g., Pharmaprojects), may also be used:

5 480156S, AA861, AD1590, AFP802, AFP860, AI77B, AP504, AU8001, BPPC, BW540C, CHINOIN 127, CN100, EB382, EL508, F1044, GV3658, ITF182, KCNTEI6090, KME4, LA2851, MR714, MR897, MY309, ONO3144, PR823, PV102, PV108, R830, RS2131, SCR152, SH440, SIR133, SPAS510, SQ27239, ST281, SY6001, TA60, TAI-901 (4-benzoyl-1-
10 indancarboxylic acid), TVX2706, U60257, UR2301, and WY41770.

Finally, NSAIDs which may also be used include the salicylates, specifically acetyl salicylic acid and the phenylbutazones, and pharmaceutically
15 acceptable salts thereof.

In addition to indomethacin, other preferred NSAIDs are acetyl salicylic acid, diclofenac, fenbufen, fenoprofen, flurbiprofen, ibuprofen, ketoprofen, naproxen, phenylbutazone, piroxicam,
20 sulindac and tolmetin.

Pharmaceutical compositions comprising the Formula I compounds may also contain inhibitors of the biosynthesis of the leukotrienes such as are disclosed in EP 138,481 (April 24, 1985), EP 115,394
25 (August 8, 1984), EP 136,893 (April 10, 1985), and EP 140,709 (May 8, 1985), which are hereby incorporated herein by reference.

The compounds of the Formula I may also be used in combination with leukotriene antagonists such as those disclosed in EP 106,565 (April 25, 1984) and EP 104,885 (April 4, 1984) which are hereby
30 incorporated herein by reference and others known in

- 27 -

the art such as those disclosed in EP Application Nos. 56,172 (July 21, 1982) and 61,800 (June 10, 1982); and in U.K. Patent Specification No. 2,058,785 (April 15, 1981), which are hereby incorporated
5 herein by reference.

Pharmaceutical compositions comprising the Formula I compounds may also contain as the second active ingredient, prostaglandin antagonists such as those disclosed in EP 11,067 (May 28, 1980) or
10 thromboxane antagonists such as those disclosed in U.S. Pat. 4,237,160. They may also contain histidine decarboxylase inhibitors such as α -fluoromethyl-histidine, described in U.S. Pat. 4,325,961. The compounds of the Formula I may also be advantageously
15 combined with an H_1 - or H_2 -receptor antagonist, such as for instance acetamazole, aminothiadiazoles disclosed in EP 40,696 (December 2, 1981), benadryl, cimetidine, famotidine, framamine, histadyl, phenergan, ranitidine, terfenadine and like
20 compounds, such as those disclosed in U.S. Patent Nos. 4,283,408; 4,362,736; and 4,394,508. The pharmaceutical compositions may also contain a K^+/H^+ ATPase inhibitor such as omeprazole, disclosed in U.S. Pat. 4,255,431, and the like. Compounds of
25 Formula I may also be usefully combined with most cell stabilizing agents, such as 1,3-bis(2-carboxy-chromon-5-yloxy)-2-hydroxypropane and related compounds described in British Patent Specifications 1,144,905 and 1,144,906. Another useful
30 pharmaceutical composition comprises the Formula I compounds in combination with serotonin antagonists such as methysergide, the serotonin antagonists

- 28 -

described in Nature, Vol. 316, pages 126-131, 1985, and the like. Each of the references referred to in this paragraph is hereby incorporated herein by reference.

5 Other advantageous pharmaceutical compositions comprise the Formula I compounds in combination with anti-cholinergics such as ipratropium bromide, bronchodilators such as the beta
10 agonist salbutamol, metaproterenol, terbutaline, fenoterol and the like, and the anti-asthmatic drugs theophylline, choline theophyllinate and enprofylline, the calcium antagonists nifedipine, diltiazem, nitrendipine, verapamil, nimodipine, felodipine, etc. and the corticosteroids,
15 hydrocortisone, methylprednisolone, betamethasone, dexamethasone, beclomethasone, and the like.

Compounds of the present invention can be prepared according to the following methods.
20 Temperatures are in degrees Celsius.

Many syntheses of indoles are well-known in the chemical literature: see for example, "Heterocyclic compounds" Volume 25, Parts I, II, III, W.J. Houlihan (Ed.), Interscience, J. Wiley & Sons,
25 N.Y., 1979, and "The Chemistry of Indoles" by R.J. Sundberg, Academic Press, N.Y., 1970. One of the most common syntheses is known as the Fischer Indole Synthesis, and is abbreviated in the following methods as "Fischer".

30 The $-CO_2H$ and $-CO_2R^{13}$ groups in the intermediates and final products in the various methods can be transformed to other representatives

- 29 -

of Q such as $-\text{CONHS}(\text{O})_2\text{R}^{15}$, $-\text{NHS}(\text{O})_2\text{R}^{15}$, $-\text{CONR}^{16}\text{R}^{16}$, $-\text{CH}_2\text{OH}$ or tetrazol-5-yl by the methodology described in U.S. Patent 4,808,608 and in Method 8. The preparation of the pro-drug forms (Q is $-\text{CO}_2\text{R}^{18}$) from the acids may be effected by the methodology of EP 104,885.

It will be apparent to one skilled in the art that the various functional groups (R^1 , R^2 , Y, Q, etc.) must be chosen so as to be compatible with the chemistry being carried out. Such compatibility can often be achieved by protecting groups, or by specific variations in the sequence of the reactions.

When R^6 is $\text{S}-\text{R}^8$, the corresponding sulfoxides and sulfones can be prepared by oxidation of the sulfides with one or two equivalents of an oxidizing agent such as m-chloroperbenzoic acid or monoperoxyphthalic acid or oxone (Trost, J. Org. Chem., 1988, pg.532).

Many of the following methods involve a basic hydrolysis of an ester function to obtain the corresponding carboxylic acid. In all cases, the free acid is obtained by acidification of the reaction mixture with a suitable acid such as hydrochloric, sulfuric, acetic, trifluoroacetic acid, etc.

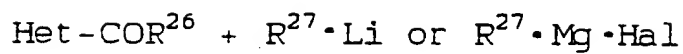
Compounds 6, 10, 11, 16, 17, 19, 23, 24, 27, 28, 29, and their precursor esters are all examples of the Formula I compounds of the present invention.

Compounds identified by Roman numerals (IV, V, XIV, XXVI, XXXI, and XXXV) are known and correspond to those compounds in EP 419,049, which is incorporated herein by reference.

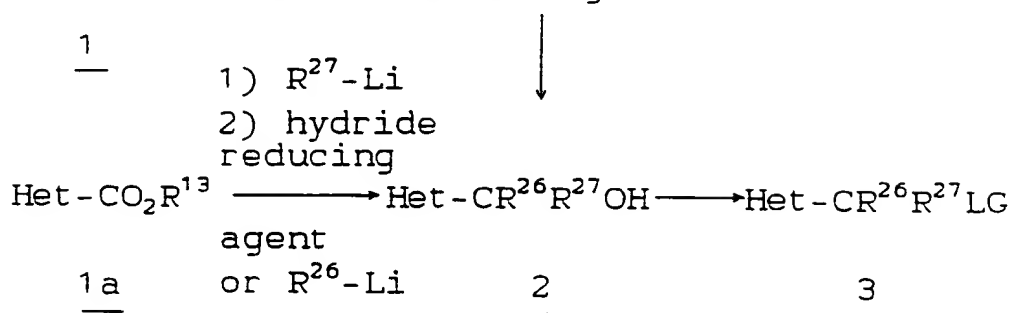
- 30 -

METHOD 1

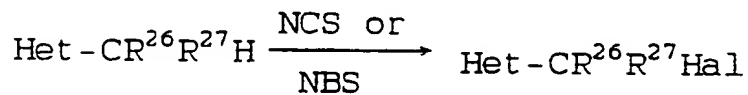
5



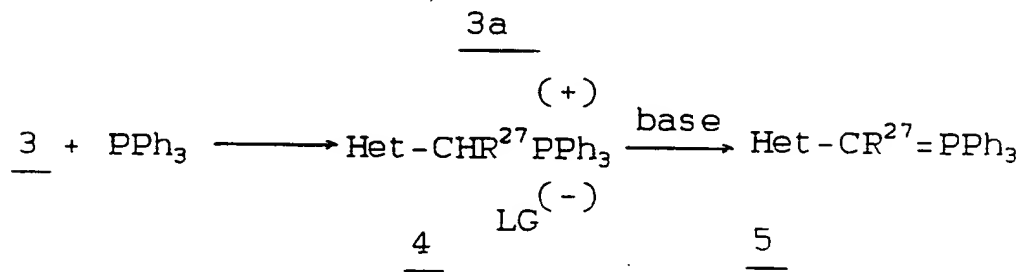
10



15



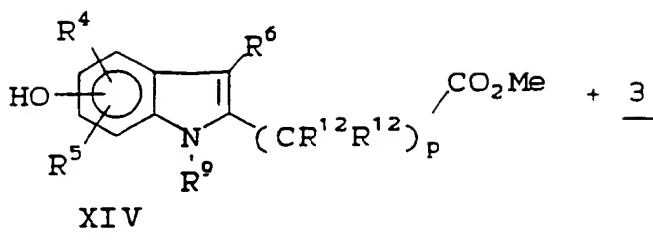
20



25

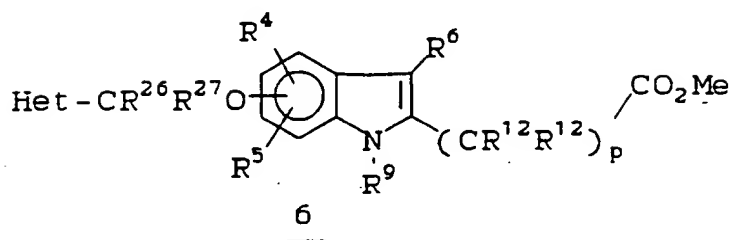
30

- 31 -

METHOD 2

10

base



20

25

30

- 32 -

Method 1

The aldehyde or ketone 1 may be converted to an alcohol 2 by reaction with an organolithium or Grignard reagent.

5 The carboxy derivative 1a may be reacted with an alkyl lithium reagent ($R^{27}Li$) followed by a suitable hydride reducing agent such as lithium aluminum hydride, sodium borohydride, DIBAL-H, or the like, or by a second alkyl lithium reagent ($R^{26}Li$) in
10 appropriate solvents such as ether, THF, hexane, toluene, or mixtures thereof, to obtain alcohol 2. The alcohol function of 2 can be converted to a suitable leaving group (LG) such as a halide, or a sulfonate ester (mesylate, tosylate, triflate, etc.)
15 by methods well known in the art to produce intermediate 3. A useful subgroup of 3 can be prepared by halogenation of the alkyl compound Het-alkyl by heating with halogenating agents such as NCS or NBS in appropriate solvents such as carbon
20 tetrachloride, benzene, and the like.

 Reaction of 3 with triphenylphosphine in ether, acetonitrile, THF, or similar solvents produces the phosphonium salt 4. Compound 4 is
25 converted into the ylid 5 by treating with a base such as Et_3N , sodium hydride, butyl lithium, or an alkoxide, depending upon the reactivity of the phosphonium salt 4.

Method 2

30 Compound 3 is reacted with phenol XIV, in the presence of a suitable base such as potassium or cesium carbonate in a suitable solvent such as

- 33 -

acetone, acetonitrile, or DMF to yield compound 6 which can be converted to its corresponding carboxylic acid by standard hydrolytic procedures.

5 An alternative synthesis of phenol XIV consists of esterifying XV (with CH_2N_2 or MeOH/H^+ or $\text{MeI}/\text{K}_2\text{CO}_3$) followed by cleavage of the quinoline group by treatment with CuCl_2 in a mixture of water and DMF heated to 60 to 90°C.

10

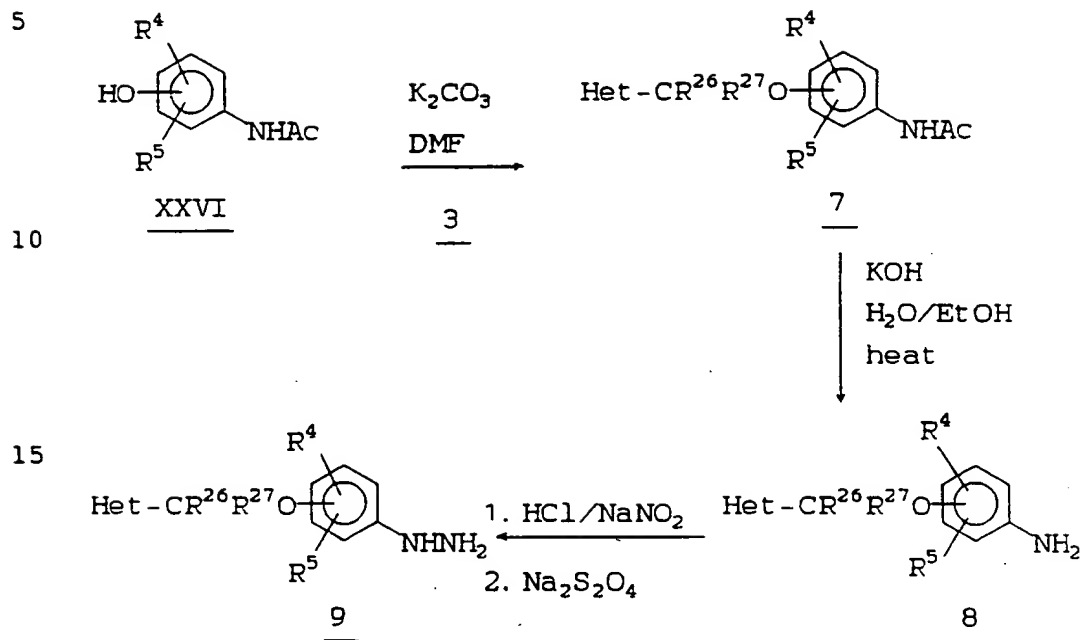
15

20

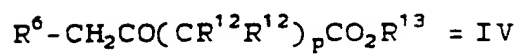
25

30

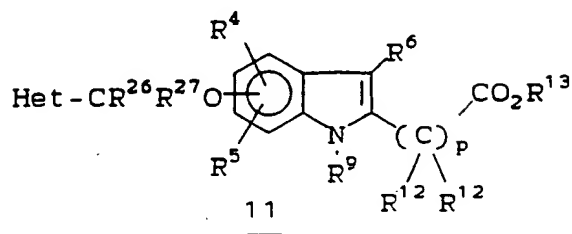
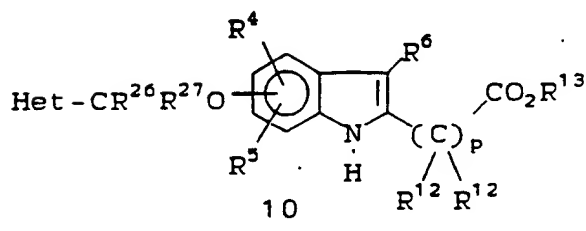
- 34 -

METHOD 3

- 35 -

METHOD 3 Cont'd.

Fischer reaction



- 36 -

Method 3

A suitable N-acetylated aminophenol XXVI is reacted with 3 using an alkali hydride or carbonate, such as potassium carbonate as a base in a polar solvent like DMF or NMP. The resulting acetanilide 7 is then de-acetylated using standard basic conditions, preferably using alcoholic potassium hydroxide under reflux to produce the aniline derivative 8. Conversion of the aniline derivative to the hydrazine analogue 9 is effected through reduction of the intermediate diazonium salt using sodium hydrosulfite in an aqueous medium.

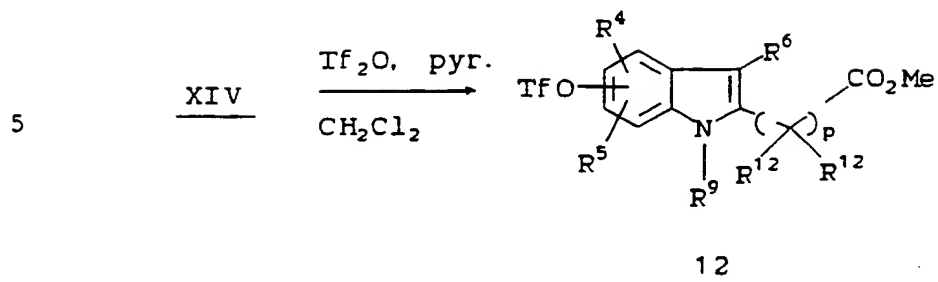
The hydrazine 9 is then processed using a Fischer indolization with ketone IV to produce compound 10, which is then alkylated on the indole nitrogen using R⁹-Hal and a suitable base such as KHMDS in THF or NaH in DMF to give compound 11.

20

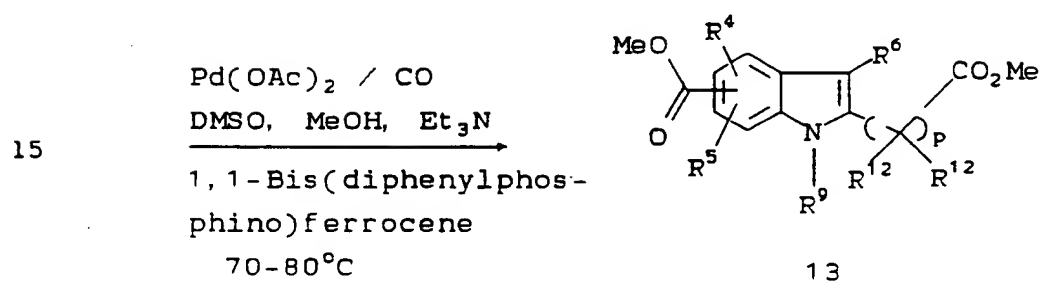
25

30

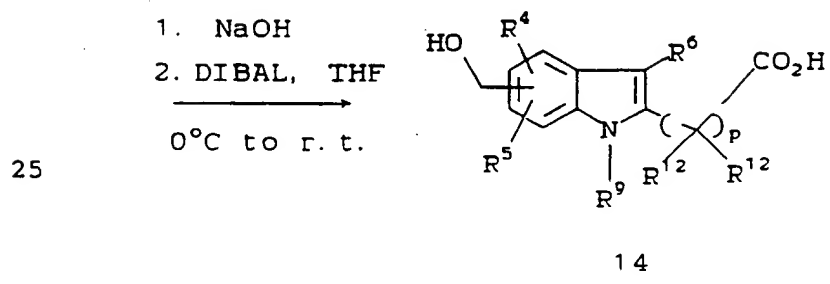
- 37 -

METHOD 4

10

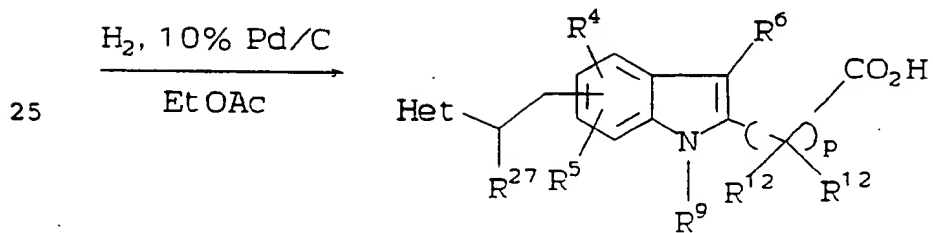
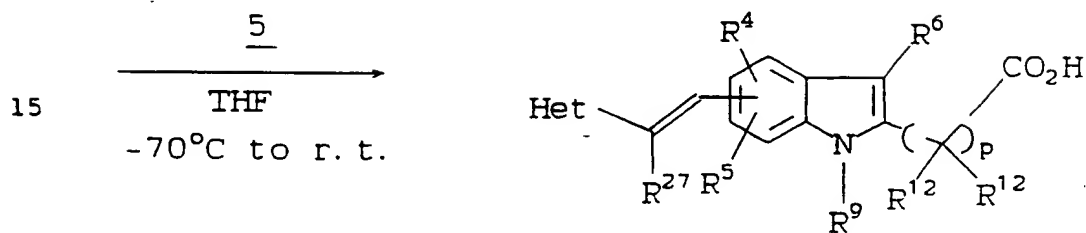
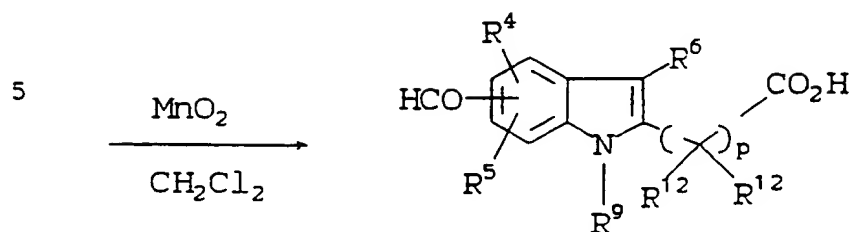


20



30

- 38 -

METHOD 4 Cont'd.

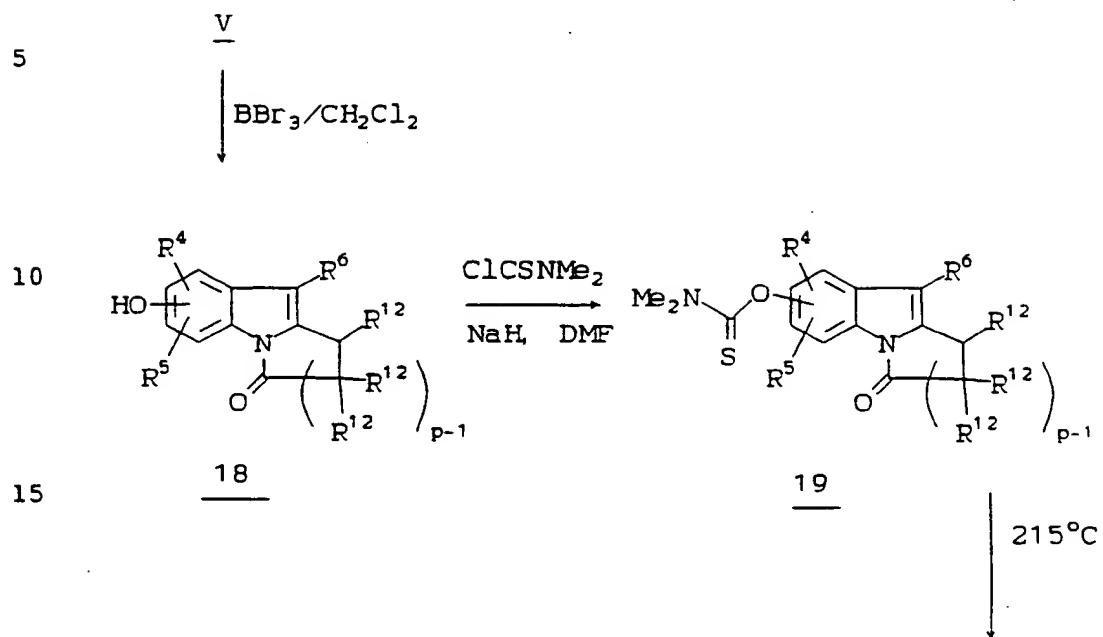
30

- 39 -

Method 4

Indole phenol XIV is transformed to a phenol triflate 12 by treatment with trifluoromethyl sulfonic anhydride (Tf_2O) in a solvent like pyridine in dichloromethane. The phenol triflate may be carboxymethylated to a compound like 13 under palladium acetate catalysis in an atmosphere of carbon monoxide, a phosphine ligand like 1,1-bis(diphenylphosphinoferrocene) enhances this reaction. Reduction of the carboxymethylated indole may be effected with a variety of hydride reducing agents. Conveniently, DIBAL-H is used in THF on the hydrolysed ester. The reduced carbinol product 14 is conveniently oxidized to a formylated derivative 15 with manganese dioxide in methylene chloride as a typical solvent. Aldehyde 15 can then be homologated under carbanion conditions, typically using Wittig reagent 5 as shown in the method, under anhydrous conditions in an etherial solvent like THF. The temperature of this reaction is typically from -70°C to room temperature. Indole styryl analogues 16 are thus formed. Further transformation of the styryl system may be effected by catalytic reduction using H_2 and Pd/C in an organic solvent like ethyl acetate to yield the saturated compound 17.

- 40 -

METHOD 5

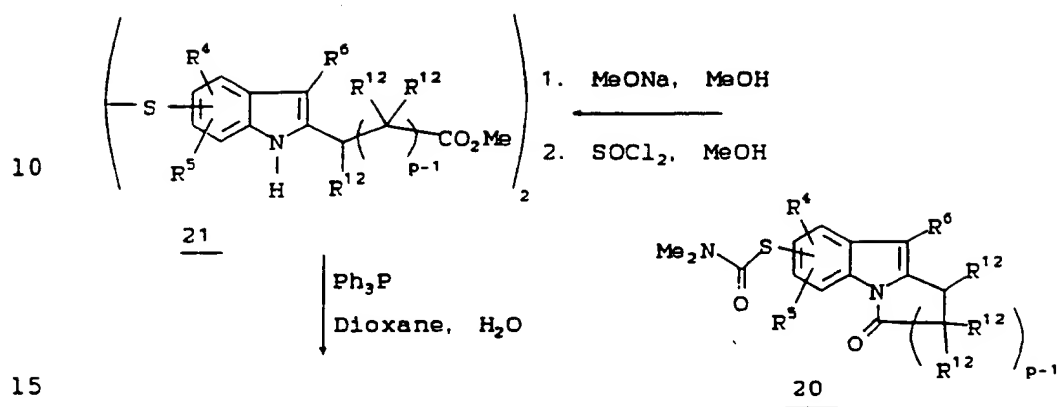
20

25

30

METHOD 5 Cont'd.

5



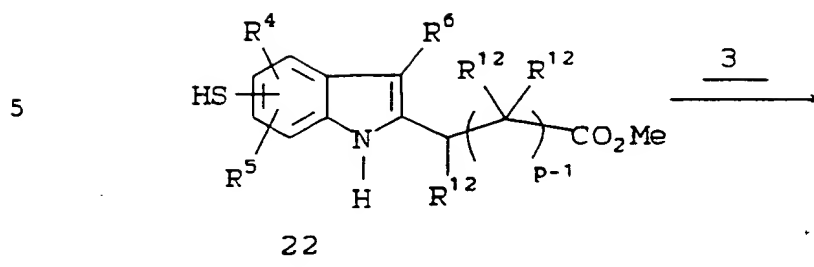
15

20

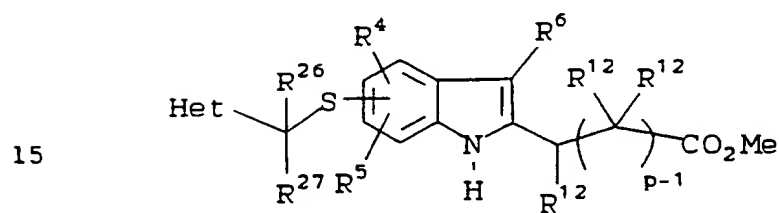
25

30

- 42 -

METHOD 5 Cont'd.

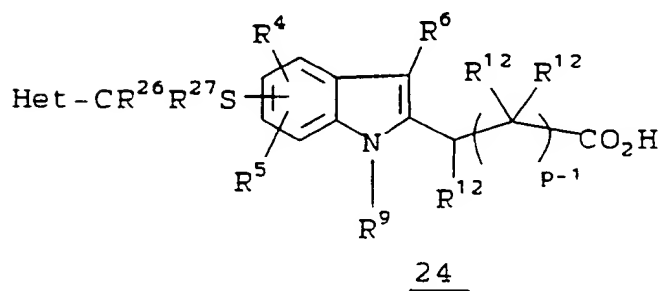
10



20

- 1) R^9 -Hal
NaH, DMF
2) hydrolysis

25



30

- 43 -

Method 5

Indole thio analogues of I such as 23 and 24 are conveniently prepared by the sequence shown in Method 5. The treatment of compound V with BBr_3 in a chlorinated solvent such as CH_2Cl_2 cleaves both the methyl ether and the indole N-benzyl group and cyclizes the product to an indole lactam 18. Derivatization of this compound as an N,N-dimethylthiocarbamoyl indole 19 followed by thermal rearrangement at $>200^\circ\text{C}$ gives rise to an N,N-dimethylcarbamoylthioindole derivative 20. Depending on the duration of heating, dethiolation ($\text{R}^6 = -\text{S}-t\text{-Bu} \rightarrow \text{R}^6 = \text{H}$) may also take place. The hydrolysis of 20 may be effected using strong base, typically sodium methoxide in methanol is used. Spontaneous formation of disulfide 21 may occur in this reaction. The reduction of 21 can be achieved using triphenylphosphine in aqueous dioxane to produce 22. Coupling of 22 to an appropriately substituted derivative 3 takes place under organic base catalysis. Typically triethylamine, in an organic solvent such as methylene chloride, is used. Transformation of indole 23 to an N-substituted derivative 24 is achieved under standard conditions described in Method 3.

- 44 -

Method 6

5

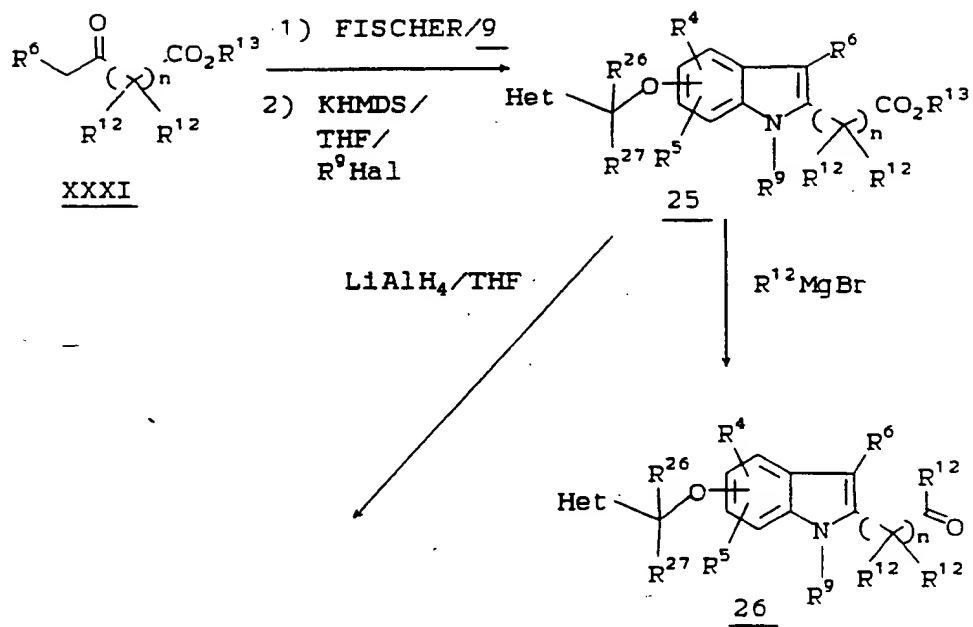
10

15

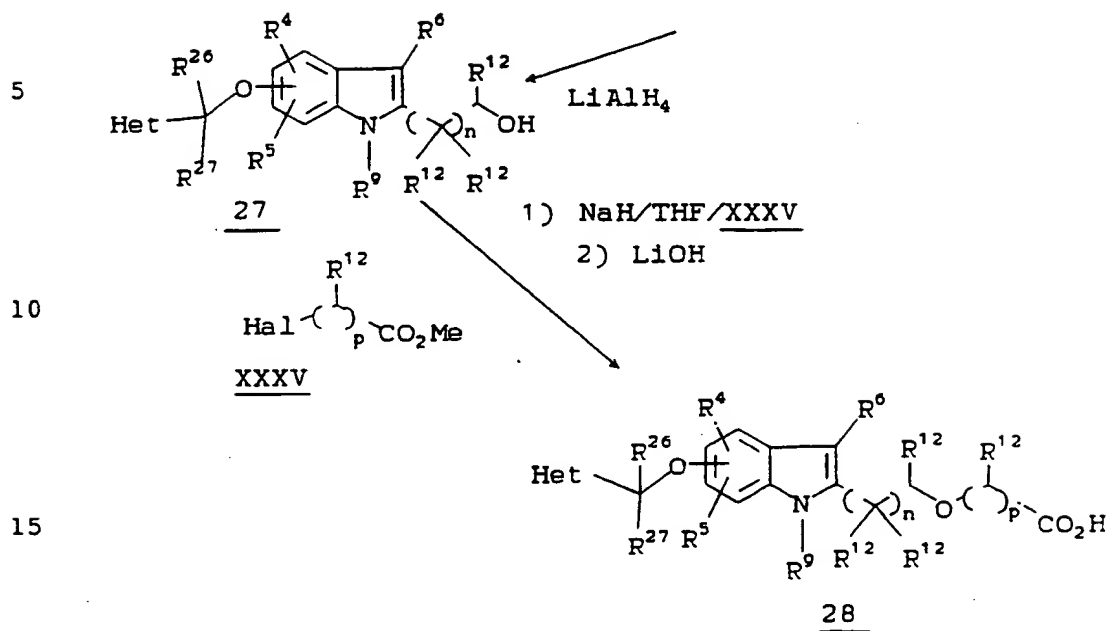
20

25

30



METHOD 6 Cont'd.



- 46 -

Method 6

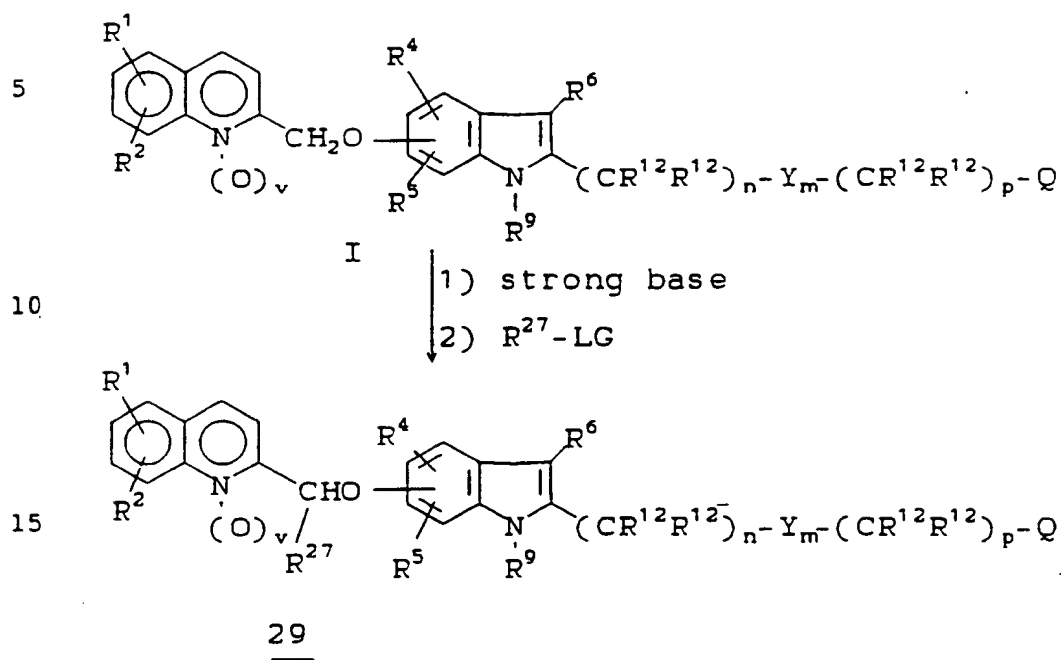
Hydrazine 2 may also be transformed directly to unsubstituted indoles by a Fischer reaction with various ketones like XXXI. N-Alkylation of the
5 indoles is effected using the conditions described in Method 3 to produce hetmethoxyindole alkanoate esters 25. Such esters are transformed to ketones or carbinols via Grignard conditions using alkyl
10 magnesium halides in ether solvents like diethyl ether or through the use of lithium aluminum hydride in ether solvents like THF. The carbinols 27 so produced may be further transformed into ester
15 compounds of the present invention by reacting with halo esters XXXV using sodium hydride as base in a suitable solvent like THF. Subsequent hydrolysis of the esters leads to acid compounds 28 of the present invention.

Method 7

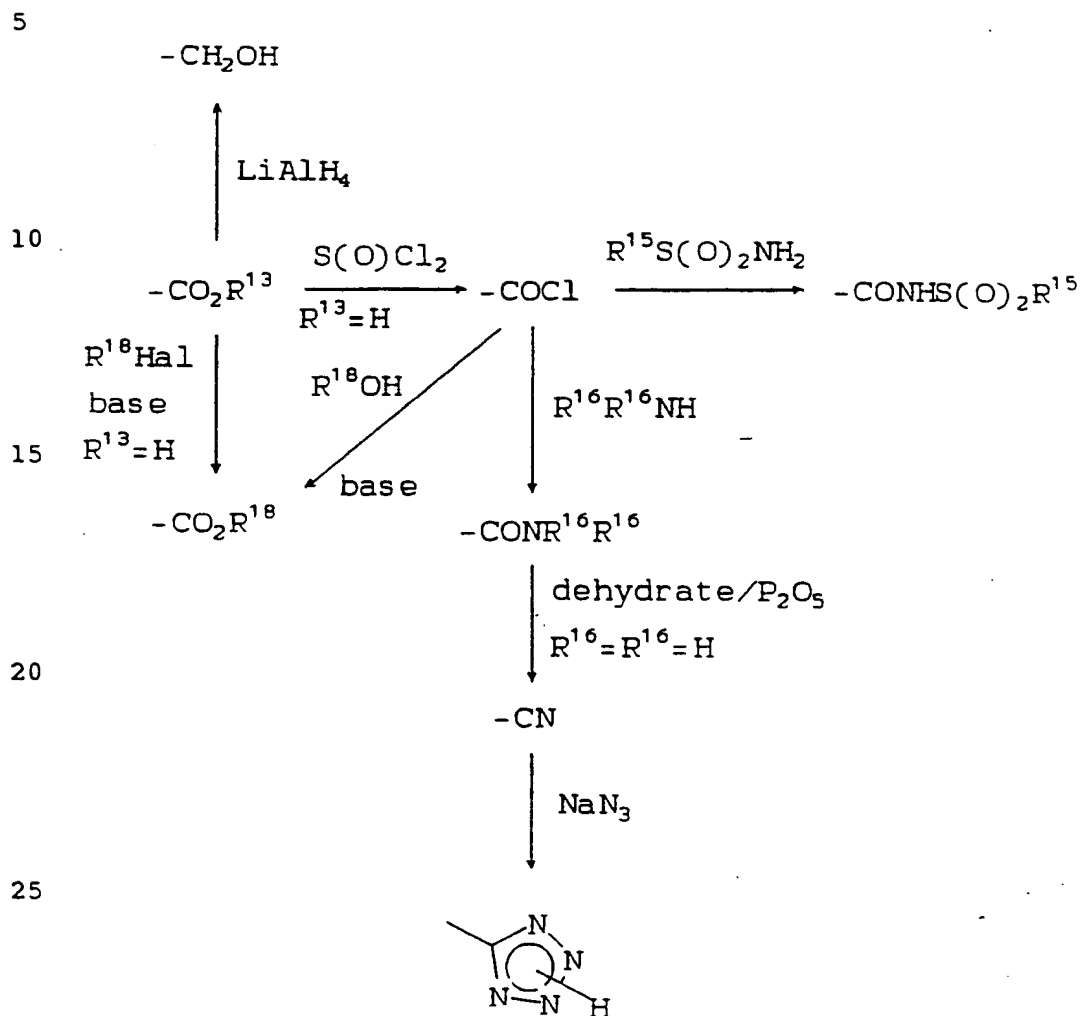
20 Compound I may be treated with a strong base such as LDA or KHMDS, in a suitable solvent or mixture of solvents such as THF, toluene, ether, methylcyclohexane, etc., followed by an alkylating
agent R^{27} -LG to give compound 29, a representative of
25 the present invention. In a similar way, other intermediates in which X^4 is $-CH_2Y^1-$ can be alkylated to provide compounds of the present invention in which X^4 is $-CHR^{27}Y^1$.

30

- 47 -

Method 7

- 48 -

METHOD 8

1H- or 2H-tetrazol-5-yl

- 49 -

Method 8

The preparation of the various definitions of Q is outlined in Method 7, starting from the readily available carboxylic acid derivative $\text{-CO}_2\text{R}^{13}$.

5 It will be obvious to one skilled in the art that many of the reactions indicated are reversible. Thus, by way of illustration, the -CN group can serve as the starting material to prepare the amide and carboxylic acid functional groups. The reactions depicted in
10 Method 7, as well as methods for synthesis of the sulfonamide group ($\text{-S(O)}_2\text{NHR}^{16}$), are well-known in the art. See, for instance, the following textbooks:

1. J. March, Advanced Organic Chemistry, 3rd ed., J.
15 Wiley and Sons, Toronto, 1985;
2. S.R. Sandler and W. Karo, Organic Functional Group Preparations, I & II, Academic Press, Toronto, 1983
and 1986.

20

Representative Compounds

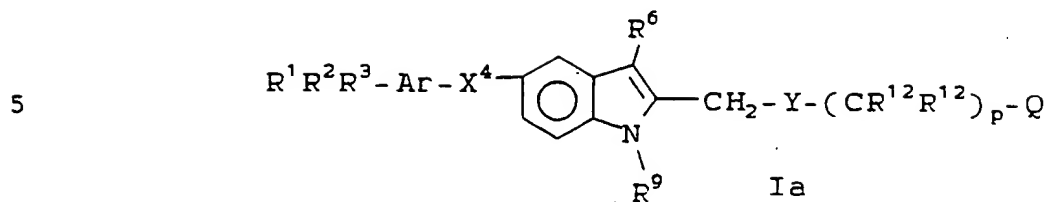
Table I illustrates compounds representative of the present invention.

25

30

- 50 -

TABLE I



Ex No.	R ¹ /R ² /R ³	Ar	X ⁴	R ⁶	R ⁹	Y-(CR ¹² R ¹²) _p -Q
15	1	H/H/H	quinolin-2-yl	CHMeO	S-t-Bu	CH ₂ Ph-4-Cl C(Me) ₂ CO ₂ Me
	1	H/H/H	quinolin-2-yl	CHMeO	S-t-Bu	CH ₂ Ph-4-Cl C(Me) ₂ CO ₂ H
	2	H/H/H	quinolin-2-yl	(-)CHMeO	S-t-Bu	CH ₂ Ph-4-Cl C(Me) ₂ CO ₂ Me
	2	H/H/H	quinolin-2-yl	(-)CHMeO	S-t-BU	CH ₂ Ph-4-Cl C(Me) ₂ CO ₂ H
	2	H/H/H	quinolin-2-yl	(+)CHMeO	S-t-Bu	CH ₂ Ph-4-Cl C(Me) ₂ CO ₂ Me
	3	H/H/H	quinolin-2-yl	(+)CHMeO	S-t-Bu	CH ₂ Ph-4-Cl C(Me) ₂ CO ₂ H
	4	H/H/H	quinolin-2-yl	CH(n-Pr)O	S-t-Bu	CH ₂ Ph-4-Cl C(Me) ₂ CO ₂ H
20	5	6-F/H/H	quinolin-2-yl	CHMeO	S-t-Bu	CH ₂ Ph-4-Cl C(Me) ₂ CO ₂ H
	6	6,7-F ₂ /H	quinolin-2-yl	CHMeO	S-t-Bu	CH ₂ Ph-4-Cl C(Me) ₂ CO ₂ H
	7	H/H/H	quinolin-2-yl	CHMeO	COCH ₂ -t-Bu	CH ₂ Ph-4-Cl C(Me) ₂ CO ₂ H
	8	H/H/H	quinolin-2-yl	(1,1-c-Pr)O	S-t-Bu	CH ₂ Ph-4-Cl C(Me) ₂ CO ₂ H
	9	H/H/H	quinazolin-2-yl	CHMeO	S-t-Bu	CH ₂ Ph-4-Cl C(Me) ₂ CO ₂ H
	10	H/H/H	quinoxalin-2-yl	CHMeO	S-t-Bu	CH ₂ Ph-4-Cl C(Me) ₂ CO ₂ H
	11	6-F/H/H	quinoxalin-2-yl	CHMeO	S-t-Bu	CH ₂ Ph-4-Cl C(Me) ₂ CO ₂ H
25	12	H/H/H	quinazolin-2-yl	CHMeO	COCH ₂ -t-Bu	CH ₂ Ph-4-Cl C(Me) ₂ CO ₂ H
	13	H/H/H	quinoxalin-2-yl	CHMeO	COCH ₂ -t-Bu	CH ₂ Ph-4-Cl C(Me) ₂ CO ₂ H
	14	H/H/H	benzimidazol-2-yl	CHMeO	S-t-Bu	CH ₂ Ph-4-Cl C(Me) ₂ CO ₂ H
	15	1-Me/H/H	benzimidazol-2-yl	CHMeO	S-t-Bu	CH ₂ Ph-4-Cl C(Me) ₂ CO ₂ H
	16	H/H/H	1,8-naphthyridin-2-yl	CHMeO	S-t-Bu	CH ₂ Ph-4-Cl C(Me) ₂ CO ₂ H
	17	H/H/H	quinoxalin-6-yl	CHMeO	S-t-Bu	CH ₂ Ph-4-Cl C(Me) ₂ CO ₂ H
	18	H/H/H	5,6,7,8-tetrahydro-quinolin-2-yl	CHMeO	S-t-Bu	CH ₂ Ph-4-Cl C(Me) ₂ CO ₂ H
30	19	1Me/H/H	Indol-6-yl	CHMeO	S-t-Bu	CH ₂ Ph-4-Cl C(Me) ₂ CO ₂ H
	20	H/H/H	imidazo[1,2-a]pyridin-2-yl	CHMeO	COCH ₂ -t-Bu	CH ₂ Ph-4-Cl C(Me) ₂ CO ₂ H
	21	H/H/H	1,6-naphthyridin-2-yl	CHMeO	S-t-Bu	CH ₂ Ph-4-Cl C(Me) ₂ CO ₂ H
	22	H/H/H	1,7-naphthyridin-2-yl	CHEtO	S-t-Bu	CH ₂ Ph-4-Cl C(Me) ₂ CO ₂ H
	23	H/H/H	5,6,7,8-tetrahydro-quinoxalin-2-yl	CHMeO	S-t-Bu	CH ₂ Ph-4-Cl C(Me) ₂ CO ₂ H

- 53 -

Samples (50 mL) of authentic LTB₄ of known concentration in radioimmunoassay buffer (RIA) buffer (potassium phosphate 1 mM; disodium EDTA 0.1 mM; Thimerosal 0.025 mM; gelatin 0.1%, pH 7.3) or PMN reaction mixture diluted 1:1 with RIA buffer are added to reaction tubes. Thereafter, [³H]-LTB₄ (10 nCi in 100 mL RIA buffer) and LTB₄-antiserum (100 mL of a 1:3000 dilution in RIA buffer) are added and the tubes vortexed. Reactants are allowed to equilibrate by incubation overnight at 4°C. To separate antibody-bound from free LTB₄, aliquots (50 mL) of activated charcoal (3% activated charcoal in RIA buffer containing 0.25% Dextran T-70) are added, the tubes vortexed, and allowed to stand at room temperature for 10 minutes prior to centrifugation (1500 x g; 10 min; 4°C). The supernatants containing antibody-bound LTB₄ are decanted into vials and Aquasol 2 (4 mL) added. Radioactivity is quantified by liquid scintillation spectrometry. The specificity of the antiserum and the sensitivity of the procedure have been described by Rokach et al. (Prostaglandins Leukotrienes and Medicine, 1984, 13, 21.) The amount of LTB₄ produced in test and control (approx. 20 ng/10⁶ cells) samples is calculated. Inhibitory dose-response curves are constructed using a four-parameter algorithm and from these the IC₅₀ values are determined.

Asthmatic Rat Assay

Rats are obtained from an inbred line of asthmatic rats. Both female (190-250 g) and male (260-400 g) rats are used.

- 54 -

Egg albumin (EA), grade V, crystallized and lyophilized, is obtained from Sigma Chemical Co., St. Louis. Aluminum hydroxide is obtained from the Regis Chemical Company, Chicago. Methysergide bimaleate is
5 supplied by Sandoz Ltd., Basel.

The challenge and subsequent respiratory recordings are carried out in a clear plastic box with internal dimensions 10x6x4 inches. The top of the box is removable; in use, it is held firmly in
10 place by four clamps and an airtight seal is maintained by a soft rubber gasket. Through the center of each end of the chamber a DeVilbiss nebulizer (No. 40) is inserted via an airtight seal and each end of the box also has an outlet. A
15 Fleisch No. 0000 pneumotachograph is inserted into one end of the box and coupled to a Grass volumetric pressure transducer (PT5-A) which is then connected to a Beckman Type R Dynograph through appropriate couplers. While aerosolizing the antigen, the
20 outlets are open and the pneumotachograph is isolated from the chamber. The outlets are closed and the pneumotachograph and the chamber are connected during the recording of the respiratory patterns. For challenge, 2 mL of a 3% solution of antigen in saline
25 is placed into each nebulizer and the aerosol is generated with air from a small Potter diaphragm pump operating at 10 psi and a flow of 8 liters/minute.

Rats are sensitized by injecting (subcutaneously) 1 mL of a suspension containing 1 mg
30 EA and 200 mg aluminum hydroxide in saline. They are

- 51 -

Assays for Determining Biological Activity

Compounds of Formula I can be tested using the following assays to determine their mammalian leukotriene biosynthesis inhibiting activity.

Rat Peritoneal Polymorphonuclear (PMN) Leukocyte Assay

Rats under ether anesthesia are injected (i.p.) with 8 mL of a suspension of sodium caseinate (6 grams in ca. 50 mL water). After 15-24 hr. the rats are sacrificed (CO₂) and the cells from the peritoneal cavity are recovered by lavage with 20 mL of buffer (Eagles MEM containing 30 mM HEPES adjusted to pH 7.4 with NaOH). The cells are pelleted (350 x g, 5 min.), resuspended in buffer with vigorous shaking, filtered through lens paper, recentrifuged and finally suspended in buffer at a concentration of 10 cells/mL. A 500 mL aliquot of PMN suspension and test compound are preincubated for 2 minutes at 37°C, followed by the addition of 10 mM A-23187. The suspension is stirred for an additional 4 minutes then bioassayed for LTB₄ content by adding an aliquot to a second 500 mL portion of the PMN at 37°C. The LTB₄ produced in the first incubation causes aggregation of the second PMN, which is measured as a change in light transmission. The size of the assay aliquot is chosen to give a submaximal transmission change (usually -70%) for the untreated control. The percentage inhibition of LTB₄ formation is calculated from the ratio of transmission change in the sample to the transmission change in the compound-free control.

- 52 -

Human Polymorphonuclear (PMN) Leukocyte LTB₄ Assay

A. Preparation of Human PMN. Human blood is obtained by antecubital venepuncture from consenting volunteers who have not taken medication within the previous 7 days. The blood is immediately added to 10% (v/v) trisodium citrate (0.13 M) or 5% (v/v) sodium heparin (1000 IU/mL). PMNs are isolated from anticoagulated blood by dextran sedimentation of erythrocytes followed by centrifugation through Ficoll-Hypaque (specific gravity 1.077), as described by Boyum (Scand. J. Clin. Lab. Invest., 21 (Supp. 97), 77(1968)). Contaminating erythrocytes are removed by lysis following exposure to ammonium chloride (0.16 M) in Tris buffer (pH 7.65), and the PMNs resuspended at 5×10^5 cells/mL in HEPES (15 mM)-buffered Hanks balanced salt solution containing Ca²⁺ (1.4 mM) and Mg²⁺ (0.7 mM), pH 7.4. Viability is assessed by Trypan blue exclusion.

B. Generation and Radioimmunoassay of LTB₄. PMNs (0.5 mL; 2.5×10^5 cells) are placed in plastic tubes and incubated (37°C, 2 min) with test compounds at the desired concentration or vehicle (DMSO, final concentration 0.2%) as control. The synthesis of LTB₄ is initiated by the addition of calcium ionophore A23187 (final concentration 10 mM) or vehicle in control samples and allowed to proceed for 5 minutes at 37°C. The reactions are then terminated by the addition of cold methanol (0.25 mL) and samples of the entire PMN reaction mixture removed for radioimmunoassay of LTB₄.

- 55 -

used between days 12 and 24 postsensitization. In order to eliminate the serotonin component of the response, rats are pretreated intravenously 5 minutes prior to aerosol challenge with 3.0 mgm/kg of methysergide. Rats are then exposed to an aerosol of 3% EA in saline for exactly 1 minute, then their respiratory profiles are recorded for a further 30 minutes. The duration of continuous dyspnea is measured from the respiratory recordings.

Compounds are generally administered either orally 1-4 hours prior to challenge or intravenously 2 minutes prior to challenge. They are either dissolved in saline or 1% methocel or suspended in 1% methocel. The volume injected is 1 mL/kg (intravenously) or 10 mL/kg (orally). Prior to oral treatment rats are starved overnight. Their activity is determined in terms of their ability to decrease the duration of symptoms of dyspnea in comparison with a group of vehicle-treated controls. Usually, a compound is evaluated at a series of doses and an ED₅₀ is determined. This is defined as the dose (mg/kg) which would inhibit the duration of symptoms by 50%.

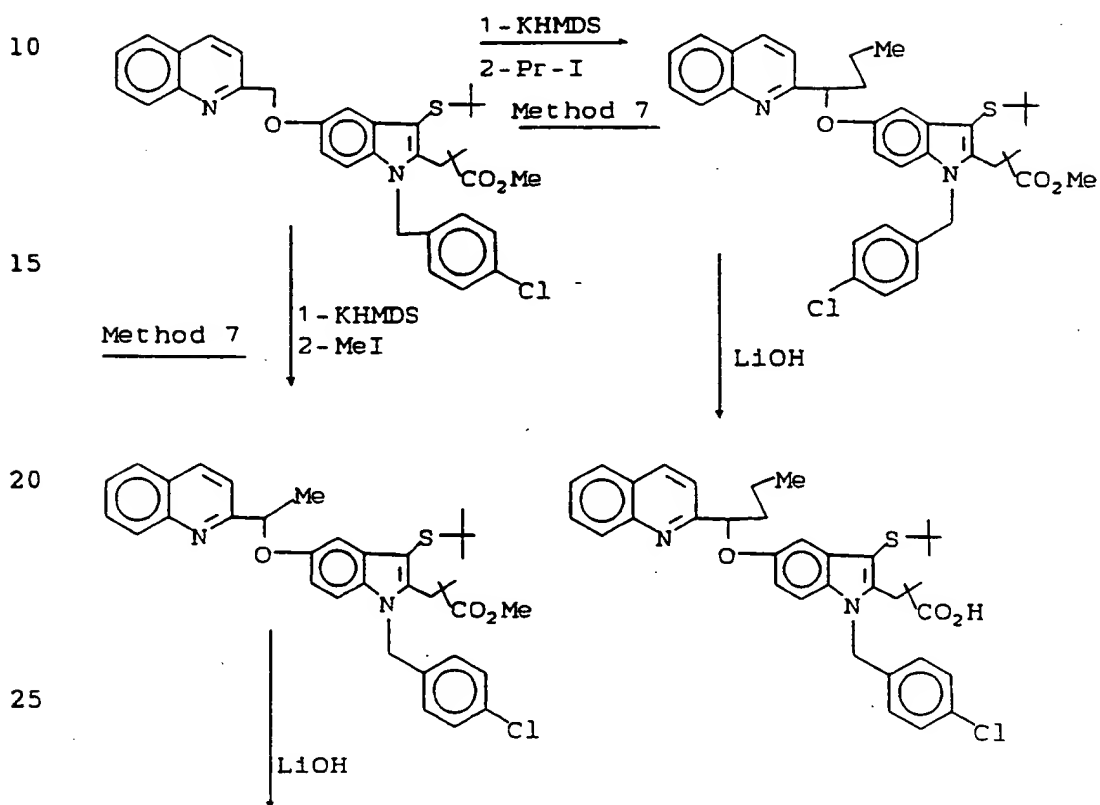
The invention is further defined by reference to the following examples, which are intended to be illustrative and not limiting. All temperatures are in degrees Celsius.

30

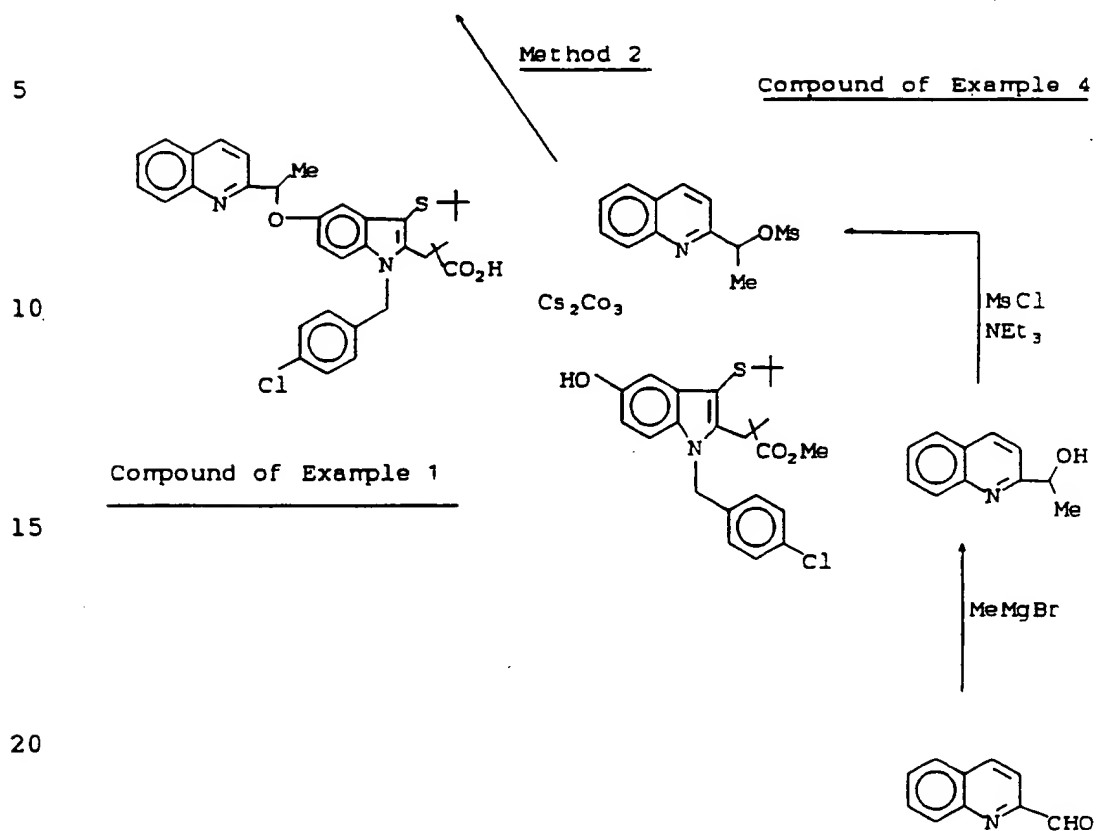
- 56 -

REACTION SCHEME 1Preparation of Compound of Example 1Preparation of Compound of Example 4

5



- 57 -

REACTION SCHEME 1 Cont'd.

- 58 -

EXAMPLE 1

(±) Sodium 3-[N-(p-chlorobenzyl)-3-(t-butylthio)-5-[1-(quinolin-2-yl)ethoxy]indol-2-yl]-2,2-dimethyl-propanoate

5

Method 1:

10

Step A: (±) Methyl 3-[N-(p-chlorobenzyl)-3-(t-butylthio)-5-[1-(quinolin-2-yl)ethoxy]indol-2-yl]-2,2-dimethylpropanoate

15

20

25

30

To a solution of methyl 3-[N-(p-chlorobenzyl)-3-(t-butylthio)-5-(quinolin-2-yl methoxy) indol-2-yl]-2,2-dimethylpropanoate (420 mg) (EP 419,049, Ex. 1, Step D) in THF (10 mL) at -78°C was added 0.6 M potassium hexamethyldisilazane in toluene (1.75 mL) and stirred at -78°C for 5 min. Then iodomethane (87 mL) was added followed 15 min later by more 0.6 M KHMDS in toluene (1.75 mL). The mixture was finally stirred at -78°C for 30 min. The reaction mixture was poured into 25% NH₄OAc (100 mL), extracted with ethyl acetate (2 x 100 mL), washed with brine (100mL), and dried (MgSO₄). The filtrate was evaporated to dryness and the residue was chromatographed on flash silica gel using ethyl

- 59 -

acetate: hexane (15:85) as eluant to give the title product as a foam.

Anal. Calc'd for $C_{36}H_{39}N_2O_3SCl$

Calc'd : C, 70.28; H, 6.39; N, 4.55

5 Found : C, 70.42; H, 6.26; N, 4.57

Step B: (\pm) Sodium 3-[N-(p-chlorobenzyl)-3-(t-butylthio)-5-[1-(quinolin-2-yl)ethoxy]indol-2-yl]-2,2-dimethylpropanoate

10 The compound (300 mg) from Step A was hydrolyzed by dissolving it in THF (3 mL), MeOH (6 mL) and 2N LiOH (1 mL). The solution was heated at 70°C for 8 h. The solution was diluted with H_2O (50 mL), acidified with glacial AcOH to pH5 and then
15 diluted with ethyl acetate (3 x 50 mL), washed with brine (50 mL), and dried ($MgSO_4$). The solution was evaporated to dryness, coevaporated with toluene (50 mL) to provide the title acid as a foam. The title compound was prepared as follows: the acid was
20 suspended in ethanol (3 mL) and treated with 1.0 N NaOH (1 equiv), diluted with H_2O (5 mL) and lyophilized to give the title product.

Anal. Calc'd for $C_{35}H_{36}N_2O_3SClNa \cdot 4H_2O$

25 Calc'd: C, 60.46; H, 6.38; N, 4.03

Found: C, 60.71; H, 6.44; N, 3.92

30

- 60 -

Method 2:Step A: 1-(Quinolin-2-yl)ethanol

To a cold (0°C) solution of quinoline-2-
5 carboxaldehyde (7.85 g) in THF (100 mL) was added
dropwise 1.4 M methyl magnesium bromide in toluene
and THF (46 mL). After total addition, the mixture
was stirred at room temperature for 30 min. The
reaction mixture was poured into aqueous saturated
10 NH₄Cl (500 mL), extracted with ethyl acetate (2 x 200
mL), washed with brine (100 mL), and dried (MgSO₄).
The solution was evaporated to dryness and
chromatographed on flash silica gel using ethyl
acetate: hexane (3:7) as eluant to yield the title
15 product as a light orange solid.

¹HNMR (250 MHz, acetone-d₆) δ 1.5 (3H, d, J = 8 Hz),
4.88 (1H, d, exchangeable), 4.92-5.08 (1H, m) 7.55
(1H, t), 7.65 (1H, d), 7.75 (1H, t), 7.92 (1H, d),
20 8.0 (1H, d), 8.3 ppm (1H, d).

Step B: 1-(Quinolin-2-yl)ethanol methanesulfonate

To a cold (-10°C) solution of alcohol from
25 Step A (346 mg) in CH₂Cl₂ (10 mL) were added
triethylamine (418 mL) and methanesulfonyl chloride
(200 mL).

30

- 61 -

The reaction mixture was stirred at room temperature for 30 min. The mixture was poured into aqueous saturated NaHCO_3 (50mL), extracted with ethyl acetate (2x50 mL), washed with brine (50mL), and dried (MgSO_4). The mixture was evaporated to dryness to give the title product as a liquid, which was used without further purification.

Step C: Methyl 3-[N-(p-chlorobenzyl)-3-(t-butylthio)-5-[1-(quinolin-2-yl)ethoxy]indol-2-yl]-2,2-dimethylpropanoate

To a solution of methyl 3-[N-(p-chlorobenzyl)-3-(t-butylthio)-5-hydroxy-indol-2-yl]-2,2-dimethylpropanoate (EP 419,049, Example 1, Step C) (460 mg) in acetonitrile (5 mL) was added solid cesium carbonate (652 mg). To this mixture was added a solution of mesylate from Step B (326 mg) in acetonitrile (3 mL) and stirred at 70°C for 1 hr. The reaction mixture was poured into 25% NH_4OAc (50 mL), extracted with ethyl acetate (2x50 mL), washed with brine (50 mL), and dried (MgSO_4). The solution was evaporated to dryness and the residue was chromatographed on flash silica gel using ethyl acetate: hexane (1:4) as eluant to give the title compound identical to the one obtained from Method 1, Step A.

30

- 62 -

Example 2

(-) Sodium 3-[N-(p-chlorobenzyl)-3-(t-butylthio)-5-[1-(quinolin-2-yl)ethoxy]indol-2-yl]-2,2,-dimethylpropanoate

5

Step A: Separation of isomers of (\pm) methyl 3-[N-(p-chlorobenzyl)-3-(t-butylthio)-5-[1-(quinolin-2-yl)ethoxy]indol-2-yl]-2,2-dimethylpropanoate

10

Both pure (-) and (+) enantiomers were obtained by HPLC separation of the title compounds on a chiralcel OD column (50cm x 2cm), hexane: 2-propanol (60:40) as eluant, with a flow rate of 5 mL/min. The retention times were 30.3 min for (-) isomer and 34.8 min for (+) isomer.

15

(-) isomer

$[\alpha]_D - 69.7 (C=1, CHCl_3)$

(+) isomer

20

$[\alpha]_D + 69.7 (C=1, CHCl_3)$

Step B: (-)Sodium 3-[N-(p-chlorobenzyl)-3-(t-butylthio)-5-[1-(quinolin-2-yl)ethoxy]indol-2-yl]-2,2-dimethylpropanoate.

25

Following the procedure of Example 1, method 1, step B, but using (-) methyl 3-[N-(p-chlorobenzyl)-3-(t-butylthio)-5-[1-(quinolin-2-yl)ethoxy]indol-2-yl]-2,2-dimethylpropanoate, the title compound was obtained.

30

- 63 -

Anal. Calc'd for $C_{35}H_{36}N_2O_3SClNa \cdot 4H_2O$
Calc'd: C, 60.46; H, 6.38; N, 4.03
Found: C, 60.55; H, 6.31; N, 3.91

$[\alpha]_D - 77.3 (C=1, CHCl_3)$ of free acid.

5

Example 3

(+) Sodium 3-[N-(p-chlorobenzyl)-3-(t-butylthio)-
5-[1-(quinolin-2-yl)ethoxy]indol-2-yl]-2,2-dimethyl-
propanoate

10

Following the procedure of Example 1, method
1, step B, but using (+) methyl 3-[N-(p-chlorobenzyl)-
3-(t-butylthio)-5-[1-(quinolin-2-yl)ethoxy]indol-2-
yl]-2,2-dimethylpropanoate from Example 2, Step A,
the title compound was obtained.

15

Anal. Calc'd for $C_{35}H_{36}N_2O_3SClNa \cdot 3H_2O$
Calc'd: C, 62.07; H, 6.25; N, 4.14
Found: C, 61.57; H, 6.41; N, 3.96.

20

$[\alpha]_D + 77.2 (C=1, CHCl_3)$ of free acid.

EXAMPLE 4

(±) Sodium 3-[N-(p-chlorobenzyl)-3-(t-butylthio)-5-
[1-(quinolin-2-yl)butoxy]indol-2-yl]-2,2-dimethyl-
propanoate

25

30

- 64 -

Following the procedure of Example 1, Method 1, Steps A and B, but using 1-iodopropane instead of methyl iodide in Step A, the title compound was obtained .

5 Anal. Calc'd for $C_{37}H_{40}N_2O_3SClNa \cdot 4H_2O$
 Calc'd: C, 61.43; H, 6.69; N, 3.87
 Found: C, 61.64; H, 6.77; N, 3.72.

10

15

20

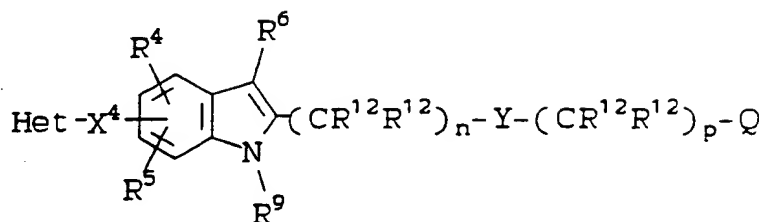
25

30

- 65 -

WHAT IS CLAIMED IS:

1. A compound of the formula I:



I

wherein:

Het is $\text{ArR}^1\text{R}^2\text{R}^3$;

15 Ar is a bicyclic aromatic 8- to 10-membered ring containing 1 to 3 N atoms, the tetrahydro derivatives thereof, and the N-oxides thereof;

20 R^1 , R^2 , R^3 , R^4 , R^5 , and R^{11} are independently hydrogen, halogen, perhalo lower alkenyl, lower alkyl, lower alkenyl, lower alkynyl, $-\text{CF}_3$, $-\text{CN}$, $-\text{NO}_2$, $-\text{N}_3$, $-\text{C}(\text{OH})\text{R}^{12}\text{R}^{12}$, $-\text{CO}_2\text{R}^{13}$, $-\text{SR}^{15}$, $-\text{S}(\text{O})\text{R}^{15}$, $-\text{S}(\text{O})_2\text{R}^{15}$, $-\text{S}(\text{O})_2\text{NR}^{16}\text{R}^{16}$, $-\text{OR}^{16}$, $-\text{NR}^{16}\text{R}^{16}$, $-\text{NR}^{13}\text{CONR}^{16}\text{R}^{16}$, $-\text{COR}^{17}$, $\text{CONR}^{16}\text{R}^{16}$, or $-(\text{CH}_2)_t\text{R}^{22}$;

25

R^6 is hydrogen, $-\text{CH}_3$, CF_3 , $-\text{C}(\text{O})\text{H}$, X^1-R^7 or X^2-R^8 ;

30 R^7 and R^{10} are independently alkyl, alkenyl, $-(\text{CH}_2)_u\text{Ph}(\text{R}^{11})_2$ or $-(\text{CH}_2)_u\text{Th}(\text{R}^{11})_2$;

- 66 -

R^8 is $-CF_3$ or R^7 ;

R^9 is hydrogen or X^3-R^{10} ;

5 each R^{12} is independently hydrogen or lower alkyl, or two R^{12} 's on same carbon atom are joined to form a cycloalkyl ring of 3 to 6 carbon atoms;

10 R^{13} is hydrogen, lower alkyl or $-CH_2R^{22}$;

R^{14} is lower alkyl or $-(CH_2)_rR^{22}$;

R^{15} is $-CF_3$ or R^{14} ;

15 R^{16} is hydrogen, OH, $-COR^{17}$, R^{14} , or two R^{16} 's on the same nitrogen may be joined to form a monocyclic heterocyclic ring of 4 to 6 atoms containing up to 2 heteroatoms chosen from
20 O, S, or N;

R^{17} is hydrogen, $-CF_3$, lower alkyl, lower alkenyl, lower alkynyl or $-(CH_2)_rR^{22}$;

25 R^{18} is $-(CH_2)_s-C(R^{19}R^{19})-(CH_2)_s-R^{20}$ or $-CH_2CONR^{16}R^{16}$;

R^{19} is hydrogen or lower alkyl;

30

- 67 -

- 5 R²⁰ is a) a monocyclic or bicyclic heterocyclic
 ring containing from 3 to 9 nuclear
 carbon atoms and 1 or 2 nuclear
 hetero-atoms selected from N, S or O
 and with each ring in the heterocyclic
 radical being formed of 5 or 6 atoms, or
 b) the radical W-R²¹;
- R²¹ is alkyl or -COR²⁴;
- 10 R²² is phenyl substituted with 1 or 2 R²³ groups;
- R²³ is hydrogen, halogen, lower alkyl, lower
 alkoxy, lower alkylthio, lower
 alkylsulfonyl, lower alkylcarbonyl, -CF₃,
15 -CN, -NO₂ or -N₃;
- R²⁴ is alkyl, cycloalkyl, or monocyclic
 monoheterocyclic ring;
- 20 R²⁵ is the residual structure of a standard amino
 acid, or R¹⁹ and R²⁵ attached to the same N
 can cyclize to form a proline residue;
- R²⁶ is hydrogen or lower alkyl;
- 25 R²⁷ is lower alkyl or R²⁶ and R²⁷ on the same
 carbon are joined to form a cycloalkyl ring
 of 3 to 6 carbon atoms;
- 30 m is 1 to 3;
 n is 0 to 3;

- 68 -

- p is 1 to 3 when m is 1;
 p is 0 to 3 when m is 0;
 r is 0 to 2;
 s is 0 to 3;
 t is 0 to 2;
 5 u is 0 to 3;
 w is 0, S or NR¹⁶
 x¹ is 0 or NR¹⁶;
 x² is CO, CR¹²R¹², S, S(O), or S(O)₂;
 x³ is CO, CR¹²R¹², S(O)₂, or a bond;
 10 x⁴ is CR²⁶=CR²⁷, CR²⁷=R²⁶, CR²⁶R²⁷Y¹, or Y¹CR²⁷R²⁶;
 Y is x¹, x², O-NR¹⁶, NR¹⁶-O or a bond;
 Y¹ is 0, S, S(O)₂, or CR²⁶R²⁶;

 Q is -CO₂R¹³, -CONHS(O)₂R¹⁵, -NHS(O)₂R¹⁵, CN,
 15 -S(O)₂NR¹⁶, -CONR¹⁶R¹⁶, -CO₂R¹⁸,
 -CONR¹⁹R²⁵, -CR¹²R¹²OH, or 1H- or
 2H-tetrazol-5-yl, -NR¹⁶R¹⁶, -NR¹⁶CONR¹⁶R¹⁶,
 -C(=NR¹⁶)R¹⁷, -NR¹⁶(CH₂)_mNR¹⁶R¹⁶,
 -N(R¹⁶)(CH₂)_mNR¹⁶CONR¹⁶R¹⁶, -CON(R¹⁶)(CH₂)_m-
 20 NR¹⁶R¹⁶, or -CON(R¹⁶)(CH₂)_mNR¹⁶CONR¹⁶R¹⁶;

or a pharmaceutically acceptable salt thereof.

2. A compound of Claim 1 wherein:

- 25 R¹ and R² are independently H or F;
 R³, R⁴, and R⁵ are hydrogen;
 R⁶ is X²-R⁸;
 R⁸ is R⁷;
 30 R⁹ is R¹⁰;

- 69 -

R¹¹ is hydrogen or halogen;

m is 0;

n is 1 to 3;

u is 0 in R⁷ and 1 in R¹⁰;

X² is CR¹²R¹² N, S or CO;

5 X⁴ is CR²⁶R²⁷-Y¹;

Y¹ is O; and

Q is -CO₂R¹³;

or a pharmaceutically acceptable salt thereof.

10

3. A compound of Claim 1

wherein:

R¹ and R² are independently H or F;

15 R³, R⁴, and R⁵ are hydrogen;

R⁶ is X²-R⁸;

R⁸ is R⁷;

R⁹ is R¹⁰;

R¹¹ is hydrogen or halogen;

20 m is 0;

n is 1 to 3;

u is 0 in R⁷ and 1 in R¹⁰;

X² is CR¹²R¹², S or CO;

X⁴ is CR²⁶R²⁷-Y¹;

25 Y¹ is O; and

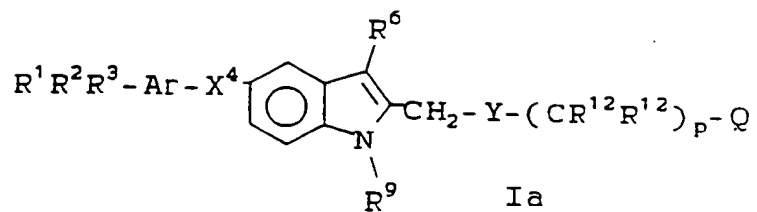
Q is 1-H- or 2H-tetrazol-5-yl;

or a pharmaceutically acceptable salt thereof.

30

- 70 -

4. A compound of Claim 1 of the formula Ia:



10

wherein the substituents are as follows:

15

20

25

30

- 71 -

Ex	R ¹ /R ² /R ³	Ar	X ⁴	R ⁶	R ⁹	Y-(CR ¹² R ¹²) _p -Q
No.						
5	1	H/H/H	quinolin-2-yl	CHMeO	S-t-Bu	CH ₂ Ph-4-Cl C(Me) ₂ CO ₂ Me
	1	H/H/H	quinolin-2-yl	CHMeO	S-t-Bu	CH ₂ Ph-4-Cl C(Me) ₂ CO ₂ H
	2	H/H/H	quinolin-2-yl	(-)CHMeO	S-t-Bu	CH ₂ Ph-4-Cl C(Me) ₂ CO ₂ Me
	2	H/H/H	quinolin-2-yl	(-)CHMeO	S-t-Bu	CH ₂ Ph-4-Cl C(Me) ₂ CO ₂ H
	2	H/H/H	quinolin-2-yl	(+)CHMeO	S-t-Bu	CH ₂ Ph-4-Cl C(Me) ₂ CO ₂ Me
10	3	H/H/H	quinolin-2-yl	(+)CHMeO	S-t-Bu	CH ₂ Ph-4-Cl C(Me) ₂ CO ₂ H
	4	H/H/H	quinolin-2-yl	CH(n-Pr)O	S-t-Bu	CH ₂ Ph-4-Cl C(Me) ₂ CO ₂ H
	5	6-F/H/H	quinolin-2-yl	CHMeO	S-t-Bu	CH ₂ Ph-4-Cl C(Me) ₂ CO ₂ H
	6	6,7-F ₂ /H	quinolin-2-yl	CHMeO	S-t-Bu	CH ₂ Ph-4-Cl C(Me) ₂ CO ₂ H
	7	H/H/H	quinolin-2-yl	CHMeO	COCH ₂ -t-Bu	CH ₂ Ph-4-Cl C(Me) ₂ CO ₂ H
15	8	H/H/H	quinolin-2-yl	(1,1-c-Pr)O	S-t-Bu	CH ₂ Ph-4-Cl C(Me) ₂ CO ₂ H
	9	H/H/H	quinazolin-2-yl	CHMeO	S-t-Bu	CH ₂ Ph-4-Cl C(Me) ₂ CO ₂ H
	10	H/H/H	quinoxalin-2-yl	CHMeO	S-t-Bu	CH ₂ Ph-4-Cl C(Me) ₂ CO ₂ H
	11	6-F/H/H	quinoxalin-2-yl	CHMeO	S-t-Bu	CH ₂ Ph-4-Cl C(Me) ₂ CO ₂ H
	12	H/H/H	quinazolin-2-yl	CHMeO	COCH ₂ -t-Bu	CH ₂ Ph-4-Cl C(Me) ₂ CO ₂ H
20	13	H/H/H	quinoxalin-2-yl	CHMeO	COCH ₂ -t-Bu	CH ₂ Ph-4-Cl C(Me) ₂ CO ₂ H
	14	H/H/H	benzimidazol-2-yl	CHMeO	S-t-Bu	CH ₂ Ph-4-Cl C(Me) ₂ CO ₂ H
	15	1-Me/H/H	benzimidazol-2-yl	CHMeO	S-t-Bu	CH ₂ Ph-4-Cl C(Me) ₂ CO ₂ H
	16	H/H/H	1,8-naphthyridin-2-yl	CHMeO	S-t-Bu	CH ₂ Ph-4-Cl C(Me) ₂ CO ₂ H
	17	H/H/H	quinoxalin-6-yl	CHMeO	S-t-Bu	CH ₂ Ph-4-Cl C(Me) ₂ CO ₂ H
25	18	H/H/H	5,6,7,8-tetrahydro-quinolin-2-yl	CHMeO	S-t-Bu	CH ₂ Ph-4-Cl C(Me) ₂ CO ₂ H
	19	1Me/H/H	Indol-6-yl	CHMeO	S-t-Bu	CH ₂ Ph-4-Cl C(Me) ₂ CO ₂ H
	20	H/H/H	imidazo[1,2-a]pyridin-2-yl	CH ₂ MeO	COCH ₂ -t-Bu	CH ₂ Ph-4-Cl C(Me) ₂ CO ₂ H
	21	H/H/H	1,6-naphthyridin-2-yl	CH ₂ MeO	S-t-Bu	CH ₂ Ph-4-Cl C(Me) ₂ CO ₂ H
	22	H/H/H	1,7-naphthyridin-2-yl	CH ₂ EtO	S-t-Bu	CH ₂ Ph-4-Cl C(Me) ₂ CO ₂ H
	23	H/H/H	5,6,7,8-tetrahydro-quinoxalin-2-yl	CH ₂ MeO	S-t-Bu	CH ₂ Ph-4-Cl C(Me) ₂ CO ₂ H

30

- 72 -

5. The compound of Claim 1 which is:

(+) Sodium 3-[N-(p-chlorobenzyl)-3-(t-butylthio)-5-[1-(quinolin-2-yl)ethoxy]indol-2-yl]-2,2-dimethylpropanoate,

5

(-) Sodium 3-[N-(p-chlorobenzyl)-3-(t-butylthio)-5-[1-(quinolin-2-yl)ethoxy]indol-2-yl]-2,2-dimethylpropanoate,

10

(+) Sodium 3-[N-(p-chlorobenzyl)-3-(t-butylthio)-5-[1-(quinolin-2-yl)butoxy]indol-2-yl]-2,2-dimethylpropanoate, or

15

(-) Sodium 3-[N-(p-chlorobenzyl)-3-(t-butylthio)-5-[1-(quinolin-2-yl)butoxy]indol-2-yl]-2,2-dimethylpropanoate, or

a pharmaceutically acceptable salt thereof.

20

6. A pharmaceutical composition comprising a therapeutically effective amount of a compound of Claim 1, 2, 3, 4 or 5 and a pharmaceutically acceptable carrier.

25

7. A pharmaceutical composition of Claim 6 additionally comprising an effective amount of a second active ingredient selected from the group consisting of non-steroidal anti-inflammatory drugs; peripheral analgesic agents; cyclooxygenase inhibitors; leukotriene antagonists; leukotriene biosynthesis inhibitors; H₁- or H₂-receptor antagonists; antihistaminic agents; prostaglandin antagonists; thromboxane antagonists; thromboxane synthetase inhibitors; and ACE antagonists.

30

- 73 -

8. A pharmaceutical composition of Claim 6, wherein the second active ingredient is a non-steroidal anti-inflammatory drug.

5 9. A pharmaceutical composition comprising a therapeutically effective amount of a compound of Claim 1, 2, 3, 4 or 5, an effective amount of a second active ingredient which is a non-steroidal anti inflammatory drug, and a pharmaceutically acceptable carrier,
10 wherein the weight ratio of said compound of Claim 1 to said second active ingredient ranges from about 1000:1 to 1:1000.

15 10. A method of preventing the synthesis, the action, or the release of SRS-A or leukotrienes in a mammal which comprises administering to said mammal an effective amount of a compound of Claim 1.

20 11. A method of Claim 10 wherein the mammal is man.

25 12. A method of treating asthma in a mammal comprising administering to a mammal in need of such treatment a therapeutically effective amount of a compound of Claim 1.

30 13. The method of Claim 12 wherein the mammal is man.

- 74 -

14. A method of treating inflammatory diseases of the eye in a mammal which comprises administering to a mammal in need of such treatment a therapeutically effective amount of a compound of Claim 1.

5

15. The method of Claim 14 wherein the mammal is man.

16. Use of a compound of claim 1, 2, 3, 4 or 5 in the manufacture of a medicament for treatment of asthma.

10

17. A compound of claim 1, 2, 3, 4 or 5 for use in medical therapy.

15

18. A leukotriene biosynthesis inhibitor pharmaceutical composition comprising an acceptable leukotriene biosynthesis inhibiting amount of a compound of claim 1, 2, 3, 4 or 5, or a pharmaceutically acceptable salt thereof, in association with a pharmaceutically acceptable carrier.

20

25

30

INTERNATIONAL SEARCH REPORT

PCT/CA 93/00253

International Application No

I. CLASSIFICATION OF SUBJECT MATTER (If several classification symbols apply, indicate all) ⁶		
According to International Patent Classification (IPC) or to both National Classification and IPC Int.Cl. 5 C07D401/12; A61K31/47		
II. FIELDS SEARCHED		
Minimum Documentation Searched ⁷		
Classification System	Classification Symbols	
Int.Cl. 5	C07D	
Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched ⁸		
III. DOCUMENTS CONSIDERED TO BE RELEVANT⁹		
Category ⁹	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claims No. ¹³
X	EP,A,0 419 049 (MERCK FROSST CANADA INC.) 27 March 1991 cited in the application * complete document * ---	1,6
X	WO,A,9 203 132 (ABBOTT LABORATORIES) 5 March 1992 cited in the application * example 288; page 77-78 * ---	1,6
P,X	EP,A,0 535 924 (MERCK FROSST CANADA INC.) 7 April 1993 see claims -----	1,6
<div style="display: flex; justify-content: space-between;"> <div style="width: 45%;"> <p>⁹ Special categories of cited documents : ¹⁰</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> </div> <div style="width: 45%;"> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"d" document member of the same patent family</p> </div> </div>		
IV. CERTIFICATION		
Date of the Actual Completion of the International Search		Date of Mailing of this International Search Report
23 AUGUST 1993		- 6. 09. 93
International Searching Authority		Signature of Authorized Officer
EUR PEAN PATENT OFFICE		VAN BIJLEN H.

**ANNEX TO THE INTERNATIONAL SEARCH REPORT
ON INTERNATIONAL PATENT APPLICATION NO.**

CA 9300253
SA 75557

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.
The members are as contained in the European Patent Office EDP file on
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

23/08/93

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A-0419049	27-03-91	AU-A- 3012692	11-02-93
		AU-B- 628212	10-09-92
		AU-A- 6121190	28-02-91
		CA-A- 2023340	23-02-91
		JP-A- 3163075	15-07-91
		US-A- 5204344	20-04-93
WO-A-9203132	05-03-92	US-A- 5095031	10-03-92
		CA-A- 2090006	21-02-92
		EP-A- 0544819	09-06-93
EP-A-0535924	07-04-93	None	